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[Intervention Review]

Tubal flushing for subfertility

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ABSTRACT

Background

Establishing the patency of the fallopian tubes is a commonly undertaken diagnostic investigation for women with subfertility. This is usually achieved by flushing contrast medium through the tubes and taking radiographs. However, it has been noted that many women conceive in the first three to six months after the tubal flushing, which has raised the possibility that tubal flushing could also be a treatment for infertility. There has been debate about which contrast medium should be used (water-soluble or oil-soluble media) as this may influence pregnancy rates.

Objectives

To evaluate the effect of flushing fallopian tubes with oil- or water-soluble contrast media on live birth and pregnancy rates in women with subfertility.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of trials, MEDLINE, EMBASE, Biological Abstracts, trial registers and reference lists of identified articles. The most recent search was conducted in June 2014.

Selection criteria

Randomised controlled trials (RCTs) comparing tubal flushing with oil-soluble or water-soluble contrast media, or with no treatment, in women with subfertility.

Data collection and analysis

Two authors independently selected the trials, assessed risk of bias and extracted data. We contacted study authors for additional information. The overall quality of the evidence was assessed using GRADE methods.

Main results

Thirteen trials involving 2914 women were included, of whom 2494 were included in the analysis.

Oil-soluble contrast media (OSCM) versus no intervention

The OSCM group had a higher rate of live birth (odds ratio (OR) 3.09, 95% CI 1.39 to 6.91, 1 RCT, 158 women, low quality evidence) and ongoing pregnancy (OR 3.59, 95% CI 2.06 to 6.26, 3 RCTs, 382 women, I^2 = 0%, low quality evidence) than women who had no intervention.

Our findings suggest that among subfertile women with a 17% chance of an ongoing pregnancy if they have no intervention, the rate will increase to between 29% and 55% if they have tubal flushing with OSCM.

Water-soluble contrast media (WSCM) versus no intervention

There was no evidence of a difference between the groups in rates of live birth (OR 1.13, 95% CI 0.67 to 1.91, 1 RCT, 334 women, very low quality evidence) or ongoing pregnancy (OR 1.14, 95% CI 0.71 to 1.84, 1 RCT, 334 women, very low quality evidence).

OSCM versus WSCM

Two RCTs reported live birth: one found a higher live birth rate in the oil-soluble group and the other found no evidence of a difference between the groups. These studies were not pooled due to very high heterogeneity (I^2 = 93%). There was no evidence of a difference between the groups in rates of ongoing pregnancy, however there was high heterogeneity (OR 1.44, 95% CI 0.84 to 2.47, 5 RCTs, 1454 women, I^2 = 76%, random-effects model, very low quality evidence).

OSCM plus WSCM versus WSCM alone

There was no evidence of a difference between the groups in rates of live birth (OR 1.06, 95% CI 0.64 to 1.77, 1 RCT, 393 women, very low quality evidence) or ongoing pregnancy (OR 1.23, 95% CI 0.87 to 1.72, 4 RCTs, 633 women, I^2 = 0%, low quality evidence).

There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies.

Authors' conclusions

The evidence suggests that tubal flushing with oil-soluble contrast media may increase the chance of pregnancy and live birth compared to no intervention. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power. There was insufficient evidence on adverse events to reach firm conclusions. Further robust randomised controlled trials are needed.

PLAIN LANGUAGE SUMMARY

Tubal flushing for subfertility

Review question

Cochrane review authors assessed the evidence to see what effect flushing of the fallopian tubes has on live birth and pregnancy rates in women with subfertility.

Background

Blocked fallopian tubes usually means that it is impossible for a woman to conceive as sperm cannot reach the egg in the tube. Establishing whether the tubes are open (patent) is important and requires contrast media (dye) to be pushed through the tubes either at the time of an x-ray (a hysterosalpingogram) or during a laparoscopy (keyhole operation). It has been reported that more women conceive following tubal flushing although it is not clear why this occurs. There has also been debate about which contrast medium should be used (water-soluble or oil-soluble) as this may influence pregnancy rates.

Study characteristics

The evidence was current to June 2014. We included randomised controlled trials (RCTs) looking at the effect flushing of the fallopian tubes (with either oil-soluble or water-soluble contrast media) has on live birth and pregnancy rates in women with subfertility. Such women were those who had not been able to conceive after at least six months of unprotected sexual intercourse. We also looked at the rates of adverse events, including miscarriage and ectopic pregnancy (a pregnancy growing outside the womb) after flushing the tubes.

Key results

We included 13 RCTs (2914 women). The trials compared oil-soluble and water-soluble media with no intervention and with each other. We found evidence that tubal flushing with oil-soluble media may increase the chances of live birth and ongoing pregnancy, compared to no intervention. Our findings suggest that among subfertile women with a 17% chance of ongoing pregnancy if they have no intervention, the rate will increase to between 29% and 55% if they have tubal flushing with oil-based contrast media. We found no evidence of a difference between water-soluble contrast media and no intervention and the contrast media compared one against the other with respect to live birth and pregnancy, though there were few data for most comparisons. There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

Quality of the evidence

The overall quality of the evidence was low or very low for all comparisons. The main limitations were imprecision, risk of bias and inconsistency. There were too few studies to evaluate the risk of publication bias.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tubal flushing with oil-soluble contrast media (OSCM) versus no intervention

Tubal flushing with oil-soluble contrast media (OSCM) versus no intervention

Population: Women with subfertility
Intervention: Tubal flushing with OSCM versus no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	OSCM				
Live birth	**129 per 1000**	315 per 1000 (171 to 507)	**OR 3.09** (1.39 to 6.91)	158 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Ongoing pregnancy	**165 per 1000**	**414 per 1000** (289 to 552)	**OR 3.59** (2.06 to 6.26)	382 (3 studies)	⊕⊕⊝⊝ **low** [3,4]	
Adverse events	There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies.					

*The basis for the **assumed risk is** the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Study was unblinded but this seems unlikely to influence fertility outcomes
[2] Single study with only 32 events
[3] Two of the three RCTS did not report methods in adequate detail, and one was at high risk of attrition bias
[4] Three small RCTs, total of 77 events

Summary of findings 2. Tubal flushing with water-soluble contrast media (WSCM) versus no intervention

Tubal flushing with water-soluble contrast media (WSCM) versus no intervention

Population: Women with subfertility
Intervention: Tubal flushing with WSCM versus no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	WSCM				
Live birth	**205 per 1000**	**226 per 1000** (147 to 330)	**OR 1.13** (0.67 to 1.91)	334 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Ongoing pregnancy	**265 per 1000**	**291 per 1000** (204 to 399)	**OR 1.14** (0.71 to 1.84)	334 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
Adverse events	There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies					

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of attrition bias. Unblinded, but this seems unlikely to influence fertiilty outcomes
[2] Wide confidence intervals compatible with appreciable benefit, harm or no effect. Low event rates (72 births, 93 pregnancies)

Summary of findings 3. Tubal flushing with oil-soluble contrast media (OSCM) versus water-soluble contrast media (WSCM)

Tubal flushing with oil-soluble contrast media (OSCM) versus water-soluble contrast media (WSCM) versus no intervention

Population: Women with subfertility
Intervention: Tubal flushing with OSCM versus WSCM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	WSCM	OSCM				
Live birth	See comment	See comment	Not estimable	931 (2 studies)	See comment	High heterogeneity (I-squared 96%): studies unsuitable for pooling. One study shows benefit for OSCM, the other shows no effect. No conclusions coudl be drawn
Ongoing pregnancy	**208 per 1000**	**274 per 1000** (181 to 393)	**OR 1.44** (0.84 to 2.47)	1454 (5 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	
Adverse events	There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies					

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High heterogeneity (I^2 76%), largely attributable to a single study. No obvious reason for heterogeneity identified
[2] Wide confidence intervals compatible with substantial benefit from OSCM or with no effect
[3] No explanation was provided

Summary of findings 4. Tubal flushing with oil-soluble plus water-soluble contrast media (OSCM + WSCM) versus WSCM only

Tubal flushing with oil-soluble plus water-soluble contrast media (OSCM + WSCM) versus water-soluble contrast media (WSCM)

Population: Women with subfertility
Intervention: Tubal flushing with OSCM + WSCM versus WSCM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	WSCM	OSCM + WSCM			
Live birth	**208 per 1000**	**218 per 1000** (144 to 317)	**OR 1.06** (0.64 to 1.77)	393 (1 study)	⊕⊖⊖⊖ **very low** [1,2]
Ongoing pregnancy	**317 per 1000**	**363 per 1000** (288 to 444)	**OR 1.23** (0.87 to 1.72)	633 (4 studies)	⊕⊕⊖⊖ **low** [1,3]
Adverse events	There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies				

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Method of allocation concealment not described
[2] Wide confidence intervals compatible with substantial benefit, harm or no effect from the intervention. Single study, only 83 events
[3] Confidence intervals compatible with substantial benefit in the OCSM plus WSCM group, or with no effect; total of 227 events

BACKGROUND

Description of the condition

Establishing the patency of the fallopian tubes is a commonly undertaken diagnostic investigation for women with subfertility. This is usually achieved by flushing contrast medium through the tubes and taking radiographs. However, it has been noted that many women conceive in the first three to six months after the tubal flushing, which has raised the possibility that tubal flushing could also be a treatment for subfertility. There has been debate about which contrast medium should be used (water-soluble or oil-soluble media) as this may influence pregnancy rates.

A doubling of conception rate after a hysterosalpingogram (HSG) with oily media was reported when compared to those women who had no procedure (Weir 1951). Many reports on the therapeutic aspect of oil-soluble contrast media have been published since the 1960s. However, many of these did not have satisfactory control groups. Various agents have been used primarily for diagnostic purposes in assessing tubal patency, such as methylene blue water-soluble dye in conjunction with laparoscopy and the water-soluble contrast media (WSCM) and oil-soluble contrast media (OSCM) used for an HSG. Other agents have been used in the past primarily for therapeutic purposes, such as carbon dioxide tubal insufflation and oil injection, although these do not form part of current routine practice in most centres (Al-Fadhli 2006).

Description of the intervention

Traditionally HSGs were performed with OSCM. Their use was gradually replaced by WSCM for a number of reasons, (i) WSCM permits better imaging of the tubal mucosal folds and ampullary rugae (internal architecture of the fallopian tubes) than OSCM (Soules 1982); (ii) OSCM have a high viscosity, which results in slow filling of the fallopian tubes often necessitating an inconveniently late film after 24 hours; (iii) OSCM reabsorption is slow, leading to prolonged persistence of OSCM within the pelvic cavity; (iv) if there is accumulation of OSCM within a blocked fallopian tube a chronic inflammatory reaction, called a lipo-granuloma, may occur; this has not been reported in women with patent fallopian tubes and is not known to have long-term consequences (Acton 1988); (v) the potential consequences of intravasation of OSCM into the pelvic blood vessels and lymphatics are allergic reactions or anaphylaxis (Lindequist 1991); and (vi) WSCM are generally cheaper than OSCM.

On the other hand, irrespective of subsequent pregnancy rates, OSCM offer some advantages over WSCM, (i) the slow filling of the fallopian tubes owing to the higher viscosity of OSCM can necessitate a 'late' film but some authorities regard the 24-hour film as an advantage because of the additional information this gives, mainly in the evaluation of adhesions after slow peritoneal spillage (Bateman 1987); and (ii) less pain has been reported with OSCM than with WSCM, probably because of less chemical irritation of the peritoneum (Soules 1982).

One of the earlier descriptions of a possible beneficial therapeutic effect of OSCM came from a radiologist (Gillespie 1965). Gillespie had changed practice from OSCM to WSCM for safety reasons. A decreased pregnancy rate from 41% to 27% over the following 12 months prompted a change back to the use of oily media, and the pregnancy rate rose again to 44%. Other non-randomised controlled studies (Acton 1988; Barwin 1971; DeCherney 1980; Mackey 1971; Yaegashi 1987) supported the hypothesis of the fertility-enhancing effect of OSCM.

With the advent of fluoroscopy, screening severe adverse reactions following the use of oily media in radiology have been reduced (Lindequist 1991). The safety of HSGs with OSCM in this context has been confirmed (Nunley 1987).

Despite data suggesting a fertility-enhancing effect of tubal flushing, particularly with OSCM, this does not form part of routine current practice. There has been a reluctance to embrace this as a standard treatment, possibly relating to the following.
(a) Prior beliefs amongst clinicians which have not, to date, been sufficiently swayed by available data, the criticisms have included:
(i) that data on sexual frequency were not available for the 'flushing' versus 'no treatment' trials prior to the RCT by Johnson 2004, hence the notion that the increased pregnancy rate might be due simply to an increased sexual frequency in the group who received treatment. However, Johnson 2004 found no evidence that a change in sexual behaviour in the OSCM treatment group compared to the no treatment group led to an increased pregnancy rate;
(ii) much of the data were from trials where the interventions were performed as diagnostic tests rather than as therapeutic interventions.
(b) A trend towards in vitro fertilisation (IVF) as the panacea for all causes of subfertility.

The first systematic review in this field was published in 1994 (Watson 1994). The original Cochrane Review (Vandekerckhove 1996), first published in 1996, was an expansion and update of that review. There have since been four further updates, in 2002 (Johnson 2002), 2005 (Johnson 2005 (a), Johnson 2005 (c)), 2007 (Johnson 2007) and this current update.

How the intervention might work

There are a number of explanations behind the theory of flushing of the fallopian tubes. These are detailed in the discussion section and include the following.

(i) Flushing out debris from the fallopian tubes, therefore unblocking undamaged tubes. Such debris may not necessarily block the fallopian tube but may hinder conception or embryo transport along the fallopian tube. The observation that lipiodol tubal flushing is effective for women with confirmed tubal patency (Johnson 2004; Nugent 2002) would support this. Furthermore, there is increasing evidence that some cases of 'blocked' fallopian tubes may have been due simply to tubal plugs, dislodged by OSCM, and thus such participants could be classified on the basis of OSCM HSG findings as having unexplained subfertility.

Histological examination of resected 'obstructed' tubal segments often fails to confirm luminal occlusion (Grant 1971) but amorphous matter has been found within tubal sections (Sulak 1987) and its presence confirmed at falloposcopy (Kerin 1991). Histology of this tissue, obtained by hydrotubating the tube at falloposcopy, has revealed casts of the tube comprised of aggregates of histiocytic-like cells from the mucosal stroma.

Observational studies (Capitanio 1991; Novy 1988; Thurmond 1990) have reported a high tubal patency and pregnancy rate after selective transcervical fallopian tube catheterisation under fluoroscopic or hysteroscopic control in patients with previously

diagnosed proximal tubal obstruction on HSG with a WSCM or dye laparoscopy. This might be attributable to the 'flushing out' of isthmic plugs.

Thurmond 1990 achieved tubal patency on at least one side in 86 of 100 consecutive women with subfertility and proximal tubal obstruction, and found that 9 of 20 women who had bilateral cornual blockage and were waiting for tubal surgery or IVF conceived after using the above technique with the majority doing so in the first four cycles after selective tubal catheterisation.

(ii) Modulation of peritoneal macrophages (Johnson 1992). OSCM have been shown to alter interleukin and prostaglandin production by peritoneal macrophages (Sawatari 1993) and to modulate peritoneal macrophage activity amongst rats during phagocytosis of sperm (Mikulska 1994).

(iii) Increasing endometrial receptivity by altering endometrial leukocyte populations. The pregnancy-enhancing effect might simply lie at the level of the endometrium. For most couples unsuccessful with IVF treatment, the outcome hinges on failed implantation. It stands to reason that a treatment which substantially increases the likelihood of conception will have some effect on endometrial receptivity.

It is possible that endometrial leukocyte populations may be altered and there is increasing evidence that uterine natural killer cells play an important role in the successful development of early pregnancy (Fukui 1999). We now have evidence that uterine dendritic cell populations are influenced by flushing the murine genital tract with the OSCM lipiodol (unpublished observations).

(iv) Other theories with less supporting evidence include 'straightening' of tortuous fallopian tubes, disruption of peritubular adhesions, stimulation of tubal ciliary action, improving cervical mucus, and an iodine-induced bacteriostatic action on mucous membranes.

Why it is important to do this review

Tubal flushing is a low-cost minimally invasive investigation which is routinely undertaken during initial assessment of infertile couples. We aimed to establish whether tubal flushing is safe and effective for improving fertility outcomes in subfertile women.

OBJECTIVES

To evaluate the effect of flushing fallopian tubes with oil- or water-soluble contrast media on live birth and pregnancy rates in women with subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were included. Non-randomised studies and quasi-randomised studies were excluded.

Types of participants

Women with subfertility, defined as inability to achieve pregnancy after at least six months of regular unprotected intercourse.

Types of interventions

Tubal flushing by means of hysterosalpingography (HSG)
Tubal flushing at the time of laparoscopy
Tubal flushing at the time of HyCoSy (hysterosalpingo contrast sonography)

Control groups could receive placebo, no treatment or an alternative type of tubal flushing.

Types of outcome measures

Primary outcomes

1. Live birth per woman
2. Ongoing pregnancy per woman (preferably defined as an ultrasound-confirmed gestational sac at 12 weeks)

Secondary outcomes

3. Miscarriage per pregnancy

4. Ectopic pregnancy per pregnancy

5. Procedural pain, immediate and delayed

6. Short-term adverse events (intravasation, infection, haemorrhage)

7. Image quality, of the uterine cavity and tubal ampulla

8. Long-term complications

Search methods for identification of studies

We searched for all published and unpublished RCTs of tubal flushing for women with subfertility, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator. The most recent search was conducted in June 2014.

Electronic searches

We searched the following electronic databases, trial registers and websites:

- Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials
- MEDLINE
- EMBASE
- CENTRAL
- PsycINFO
- Biological Abstracts

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.0.2, chapter 6, 6.4.11). The EMBASE and PsycINFO searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials

Trials registers were searched for ongoing and registered trials:

- National Research Register (NRR) (www2.le.ac.uk/library/find/databases/n/nationalresearchregister);
- Current Controlled Trials (http://www.controlled-trials.com);
- NHS Centre for Reviews and Dissemination (www.crd.york.ac.uk/CRDWeb/);
- US National Institutes of Health (NHI) Clinical Trials Register (www.clinicaltrials.gov).

We searched for any trials with the following keywords:
1. hysterosalpingogram, HSG or salpingogram;
2. lipiodol or ethiodol;
3. water-soluble contrast media, WSCM, oil-soluble contrast media or OSCM;
4. tubal flushing.

The search strategies can be found in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6.

Searching other resources

We checked the citation lists of included trials, eligible studies and relevant review articles. We contacted the first or corresponding authors of trials eligible for inclusion to ascertain if they were aware of any ongoing or unpublished trials.

We searched abstract booklets from scientific meetings, including the European Society of Human Reproduction and Embryology, the World Congress of IVF and Reproductive Genetics, the British Fertility Society, the Fertility Society of Australia and the British Congress of Obstetrics and Gynaecology.

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, we retrieved the full texts of all potentially eligible studies. Two review authors (LM and AH) independently selected the trials for inclusion. Differences of opinion were resolved by consensus after consultation with the other review author (AJW).

Data extraction and management

Two of the review authors (LM and AH) independently extracted data, and differences of opinion were resolved by consensus. We sought additional information on trial methodology or actual original trial data from the corresponding authors of trials which appeared to meet the eligibility criteria if aspects of methodology were unclear, or if data were in a form unsuitable for meta-analysis.

Assessment of risk of bias in included studies

Two review authors (LM and AH) independently assessed the included studies using the Cochrane risk of bias assessment tool. Disagreements were resolved by discussion. The conclusions were presented in the 'Risk of bias' table (and for summary see Figure 1 and Figure 2) and incorporated into the interpretation of review findings by means of sensitivity analyses.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

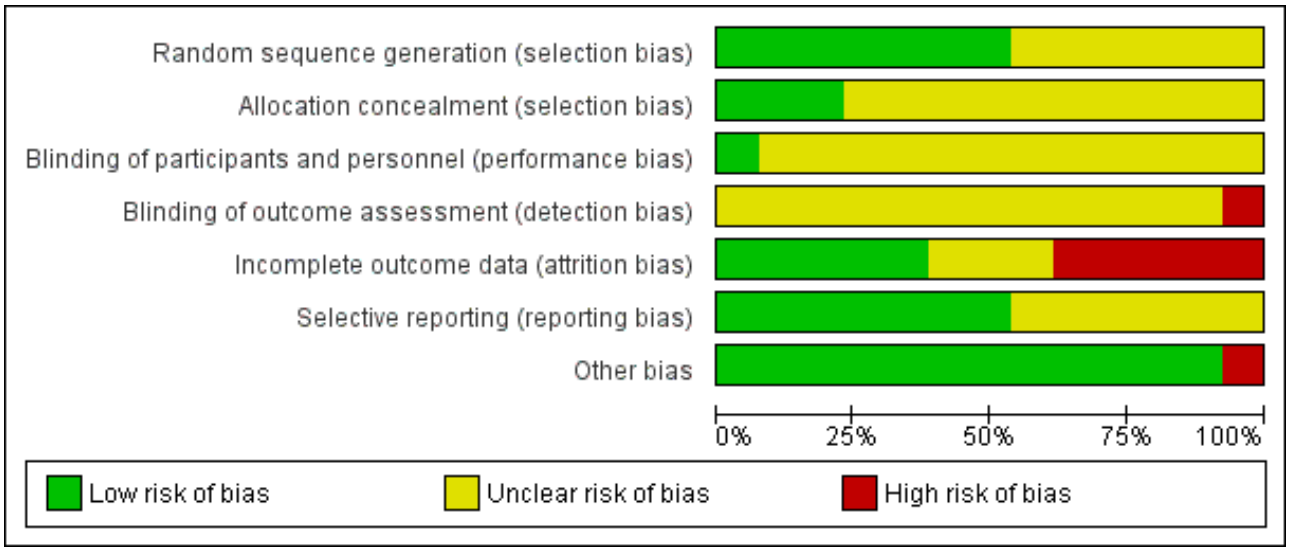
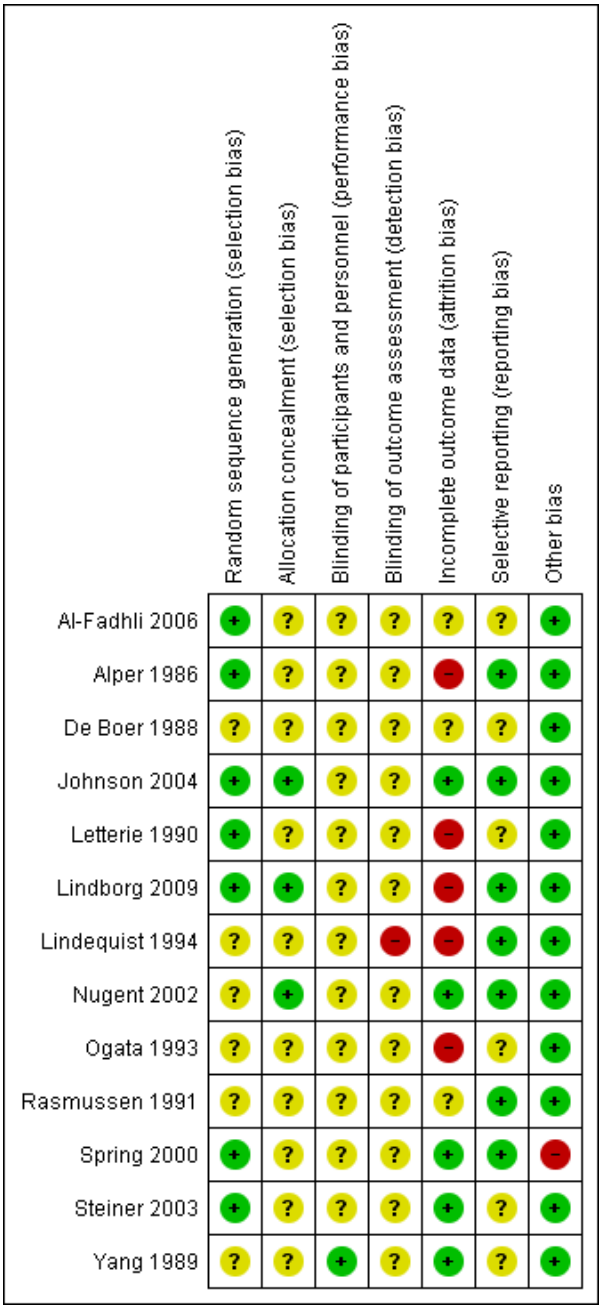


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

For dichotomous data the numbers of events in the control and intervention groups of each study were used to calculate Mantel-Haenszel odds ratios (ORs) and 95% confidence intervals (95% CI).

For continuous data (for example procedural pain), mean differences (MDs) and 95% CIs were calculated.

Unit of analysis issues

The primary analysis was per woman randomised. Miscarriage and ectopic pregnancy were analysed per pregnancy.

Dealing with missing data

The data were analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original investigators. Where these were unobtainable, imputation of individual values was undertaken for the primary outcomes only. Live births were assumed not to have occurred in participants with unreported outcomes.

Assessment of heterogeneity

Statistical heterogeneity between the results of different studies was examined by checking the results of Chi^2 tests and the I^2

percentage value. If the I^2 was > 50% and Chi^2 P value < 0.05, indicating substantial heterogeneity, this was addressed through sensitivity analysis. If I^2 was > 80%, then the data were not pooled in a meta-analysis.

If statistical heterogeneity was present, although the results were pooled, reasons for the heterogeneity were sought and the meta-analysis results interpreted cautiously.

As part of the heterogeneity assessment we carried out a set of a priori defined subgroup analyses.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies. If there were 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

If the studies were sufficiently similar, we combined the data using a fixed-effect model in the following comparisons.

- Tubal flushing with OSCM versus no treatment.
- Tubal flushing with WSCM versus no treatment.
- Tubal flushing with OSCM versus WSCM.
- Tubal flushing with OSCM and WSCM versus WSCM alone.

An increase in the odds of a particular outcome (which may be beneficial, for example in the case of live birth; or detrimental, for example in the case of a complication) was displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome was displayed graphically to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed to determine whether findings differed in studies performed mainly for diagnostic reasons as opposed to studies performed mainly for therapeutic reasons.

If we detected significant heterogeneity (defined as P < 0.05 in the Chi^2 heterogeneity test), we explored possible explanations in sensitivity analyses. We used a random-effects model if significant heterogeneity was present.

Sensitivity analysis

A priori, we planned the following sensitivity analyses for the primary outcomes:

a) restricting the analysis to studies at low risk of bias;

b) using alternative imputation methods;

c) based on the source of data (whether it was a diagnostic or a therapeutic study);

d) using risk ratios instead of odds ratios;

e) using a random-effects model instead of a fixed-effect model.

RESULTS

Description of studies

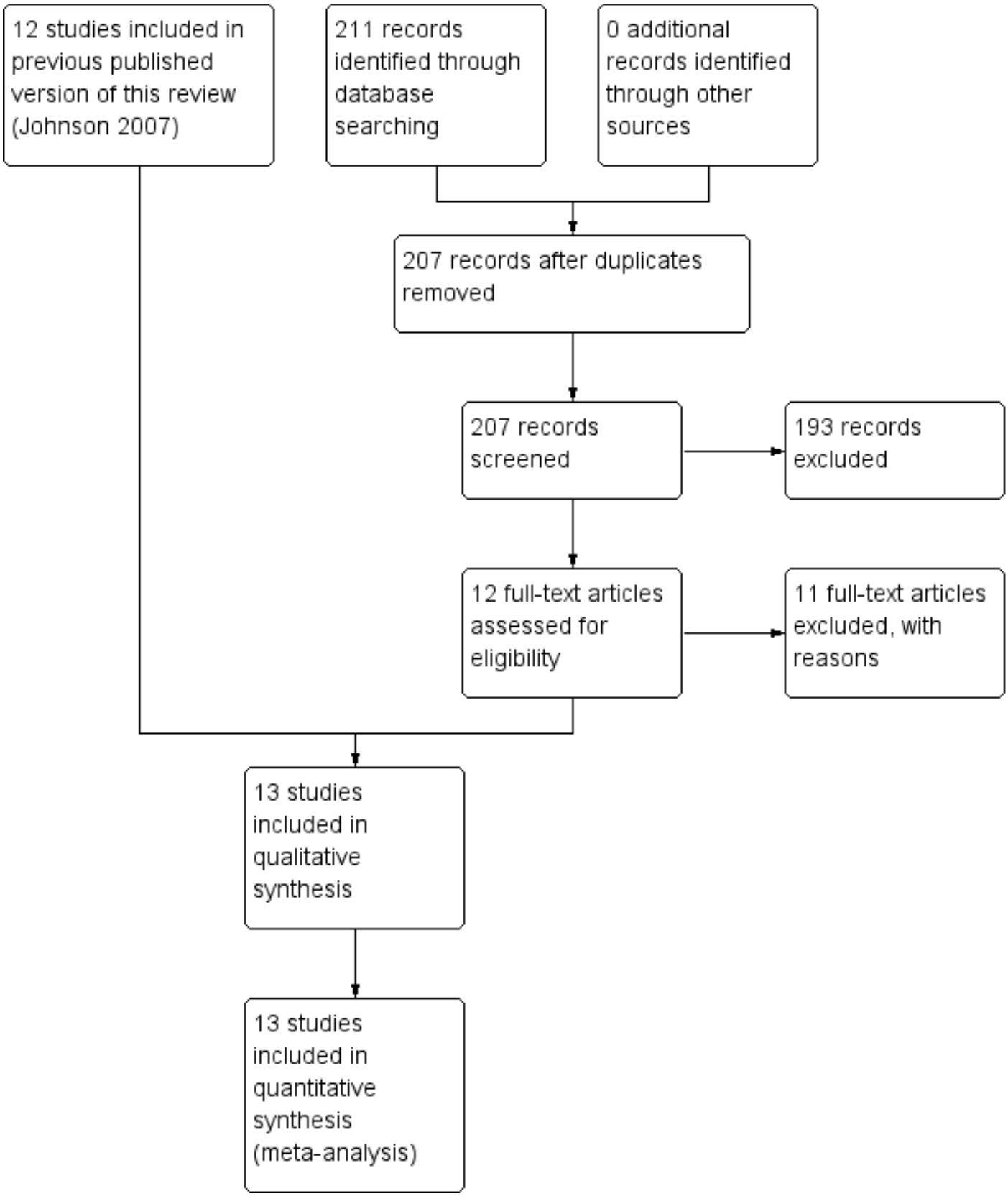
Results of the search

The 2014 search retrieved 207 discrete articles. Eleven studies were potentially eligible and were retrieved in full text for further consideration. One study (Lindborg 2009) met our inclusion criteria and 10 were excluded. See Characteristics of excluded studies.

Twelve studies were included in previous versions of the review, so the updated version included 13 studies (2582 analysed participants). See Characteristics of included studies.

See Figure 3 for details of the screening and selection process.

Figure 3. Study flow diagram.



Included studies

Types of studies

The 13 included studies were all parallel group RCTs:

- six trials were conducted primarily for therapeutic reasons (Al-Fadhli 2006; Johnson 2004; Letterie 1990; Lindborg 2009; Nugent 2002; Steiner 2003);
- seven trials were conducted primarily for diagnostic reasons (Alper 1986; De Boer 1988; Lindequist 1994; Ogata 1993; Rasmussen 1991; Spring 2000; Yang 1989).

Types of interventions

- Three trials including 382 analysed participants assessed tubal flushing with OSCM versus no treatment (Johnson 2004; Nugent 2002; Ogata 1993).
- One trial assessed tubal flushing with WSCM versus no treatment (Lindborg 2009).
- Six trials with 1483 participants assessed flushing with contrast which included OSCM versus flushing with WSCM alone (OSCM versus WSCM) (Alper 1986; De Boer 1988; Letterie 1990; Lindequist 1994; Rasmussen 1991; Spring 2000).
- Three trials (Al-Fadhli 2006; Steiner 2003; Yang 1989) compared OSCM + WSCM versus WSCM tubal flushing. Spring 2000 also included an arm receiving tubal flushing with both WSCM and OSCM. These four trials included a total of 633 participants for this comparison.

The included studies and their methodological details are summarised in the table Characteristics of included studies.

Types of participants

Women or couples with unexplained infertility were considered eligible for inclusion. Thirteen studies with a total of 2582 analysed participants were included in this review. The number of participants in each study ranged from 34 (Nugent 2002) to 666 (Spring 2000).

The duration of infertility was at least six months in all but three trials where duration of infertility was not specified (Al-Fadhli 2006; Ogata 1993; Yang 1989).

The mean age or age range was not stated in two trials (Ogata 1993; Rasmussen 1991) and the exclusion criteria were not stated in four trial comparisons (Johnson 2004; Letterie 1990; Spring 2000; Spring 2000).

The remaining trials based their exclusion criteria on iodine allergy (Al-Fadhli 2006), bilateral tubal blockage (Alper 1986; Lindborg 2009; Ogata 1993), previous infertility surgery (De Boer 1988), male factor infertility, suspected anovulation (Lindborg 2009), technical difficulties with the HSG (Lindequist 1994; Rasmussen 1991) and causes of infertility other than unexplained (Nugent 2002).

Type of outcome measures

Primary outcomes

Our primary outcomes were live birth and ongoing pregnancy. Four studies reported live birth (Johnson 2004; Lindborg 2009; Rasmussen 1991; Spring 2000). All 13 studies reported ongoing pregnancy.

Secondary outcomes

Four studies reported miscarriage (Johnson 2004; Letterie 1990; Lindborg 2009; Spring 2000).

Three studies reported ectopic pregnancy (Johnson 2004; Lindborg 2009; Spring 2000).

Two reported procedural pain (Alper 1986; Lindequist 1994).

Two reported short-term adverse events (Alper 1986; Lindequist 1994).

One reported image quality (De Boer 1988).

None reported long-term complications.

Excluded studies

Ten studies were excluded from the review: one was not truly randomised with the use of alternate assignment (Schwabe 1983), five were non-randomised comparative studies of HSG with OSCM versus WSCM (Acton 1988; Barwin 1971; DeCherney 1980; Gillespie 1965; Yaegashi 1987), one was a three-way non-randomised comparative study of HSG with OSCM versus WSCM versus no treatment (Mackey 1971), and one did not report pregnancy outcomes (Wolf 1989). Another was a recent observational study of pregnancy rates in women undergoing HSG with OSCM (Court 2014). See Characteristics of excluded studies.

Risk of bias in included studies

See Characteristics of included studies; Figure 1; Figure 2.

Allocation

Sequence generation

Seven trials were rated as at low risk of bias in this domain as they used computer-generated lists or random number tables (Al-Fadhli 2006; Alper 1986; Johnson 2004; Letterie 1990; Lindborg 2009; Spring 2000; Steiner 2003). The method of sequence generation was not adequately described in seven studies, which were rated as at unclear risk of bias (Alper 1986; De Boer 1988; Lindequist 1994; Nugent 2002; Ogata 1993; Rasmussen 1991; Yang 1989).

Allocation concealment

Adequate concealment of assigned treatment prior to allocation was reported in three trials (Johnson 2004; Lindborg 2009; Nugent 2002) which were rated as at low risk of bias in this domain. Ten studies did not clearly report an adequate method of allocation concealment and were rated as at unclear risk (Al-Fadhli 2006; Alper 1986; De Boer 1988; Letterie 1990; Lindequist 1994; Ogata 1993; Rasmussen 1991; Spring 2000; Steiner 2003; Yang 1989).

Blinding

Only one trial (Yang 1989) was double-blinded, though it was not specifically stated that outcome assessment was blinded. None of the other trials stated that blinding was used, although participant blinding would have been possible in trials where different contrast media were compared. All trials could have been single-blinded for the investigators assessing outcomes. Our primary outcome (live birth and ongoing pregnancy) may not be unduly prone to bias related to lack of blinding, but there may be scope for bias related to more thorough follow up by investigators to find outcomes in

couples not attending follow-up clinics. All studies were rated as at unclear risk of bias in this domain.

Incomplete outcome data

Randomisation was undertaken some time in advance of the tubal flushing procedure itself (at referral and at scheduling) in four trials (Lindborg 2009; Lindequist 1994; Ogata 1993; Rasmussen 1991) and subsequently a number of participants were withdrawn before they underwent the HSG because they had conceived, changed their mind about undergoing the procedure or participating in the trial, or were subsequently found not to fulfil the criteria for the trial. Randomisation immediately before the procedure was more appropriate.

Withdrawals and losses to follow up after HSG varied from 0% (Nugent 2002; Yang 1989), 1% (Spring 2000), 3% (Johnson 2004), 5% (Steiner 2003), 9% (Rasmussen 1991), 11% (Al-Fadhli 2006), 19% (Alper 1986), 21% (Lindequist 1994), 22% (Lindborg 2009), 28% (Letterie 1990) and 37% (Ogata 1993) of participants who underwent the procedure; this was unclear for one trial (De Boer 1988). The highest withdrawal rate of 37% (Ogata 1993) was due to the fact that women underwent the HSG (or not) before any results of their other investigations were known, and only women with proof of ovulation in all four cycles of follow up were retained in the analysis. Incompleteness or loss to follow up accounted for approximately one half of the withdrawals in the other trials.

Other than in the trials where all randomised participants were analysed, it was impossible to recalculate the treatment effect based on the originally randomised groups (using the intention-to-treat principle). It was not obvious that the intention-to-treat principle was the best approach for analysis given the poor design (randomisation before eligibility established) of some of the trials. However, it is generally recommended to minimize bias in the design, conduct and analysis of RCTs of effectiveness. Only two trials (Johnson 2004; Nugent 2002;) performed an intention-to-treat analysis. Only one trial (Alper 1986) specified outcome details for participants withdrawn from each randomised group. Recalculation of the OR including these participants had little effect on the conclusions of this trial (OR 1.31, 95% CI 0.51 to 3.04 for all participants versus OR 1.31, 95% CI 0.56 to 3.09 after exclusion).

Selective reporting

All studies reported live birth or pregnancy, or both. However, five studies failed to report any adverse events (Al-Fadhli 2006; De Boer 1988; Ogata 1993; Steiner 2003; Yang 1989) and one did not clearly report how pregnancy was ascertained (Letterie 1990). These studies were rated as at unclear risk of selctive reporting, while others were rated as at low risk.

Other potential sources of bias

We found no potential sources of within-study bias in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Tubal flushing with oil-soluble contrast media (OSCM) versus no intervention; **Summary of findings 2** Tubal flushing with water-soluble contrast media (WSCM) versus no intervention; **Summary of findings 3** Tubal flushing with oil-soluble contrast media (OSCM) versus water-soluble contrast media (WSCM); **Summary of findings 4** Tubal flushing with oil-soluble plus water-soluble contrast media (OSCM + WSCM) versus WSCM only

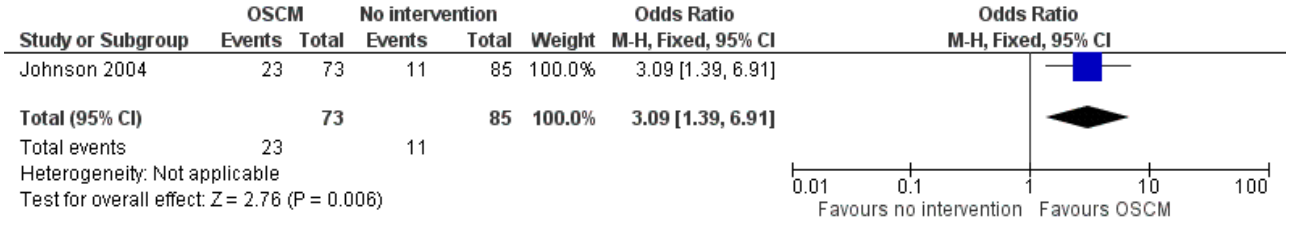
(1) Tubal flushing with OSCM versus no treatment

Primary outcomes

1.1 Live birth

Only one study (Johnson 2004) making this comparison reported live birth. Tubal flushing with OSCM was associated with a significant increase in the odds of ongoing pregnancy (OR 3.09, 95% CI 1.39 to 6.91, 1 RCT, 158 women). See Analysis 1.1; Figure 4.

Figure 4. Forest plot of comparison: 1 OSCM versus no intervention, outcome: 1.1 Live birth.



1.2 Ongoing pregnancy

Three studies (Johnson 2004; Nugent 2002; Ogata 1993) making this comparison reported ongoing pregnancy (OR 3.59, 95% CI 2.06 to 6.26, 3 RCTs, 382 women, I^2 = 0%). See Analysis 1.2.

Subgroup analysis

Findings were similar in trials either with a diagnostic or with a therapeutic focus.

- In trials where the intervention was intended primarily as a diagnostic test (Ogata 1993): pregnancy OR 3.48 (95% CI 1.42 to 8.52).
- In trials where the intervention was intended primarily as a therapy (Johnson 2004; Nugent 2002): pregnancy OR 3.67 (95% CI 1.81 to 7.44).

Sensitivity analyses

None of the planned sensitivity analyses substantially altered the main findings.

Secondary outcomes

1.3 Miscarriage per pregnancy

Only one study (Johnson 2004) reported miscarriage rate per pregnancy. There was no evidence of a difference between the

groups (OR 1.00, 95% CI 0.16 to 6.25, 1 RCT, 42 pregnancies). See Analysis 1.3.

1.4 Ectopic pregnancy

Only one study (Johnson 2004) reported ectopic pregnancy. There was no evidence of a difference between the groups (OR 1.58, 95% CI 0.06 to 41.34, 1 RCT, 42 pregnancies). See Analysis 1.5.

1.5 Procedural pain, immediate and delayed

This outcome was not reported.

1.6 Short-term adverse events (intravasation, infection, haemorrhage)

One study (Johnson 2004) reported 2 cases of asymptomatic intravasation without sequelae in the OSCM group (n = 73) and no other adverse events. Nugent 2002 also stated there were no adverse events. The remaining studies in this group did not report on these outcomes.

1.7 Image quality, of the uterine cavity and tubal ampulla

This outcome was not reported.

1.8 Long-term complications

Two studies in this group (Johnson 2004; Nugent 2002) stated that there were no long-term complications. This outcome was not reported in the remaining studies.

(2) Tubal flushing with WSCM versus no treatment

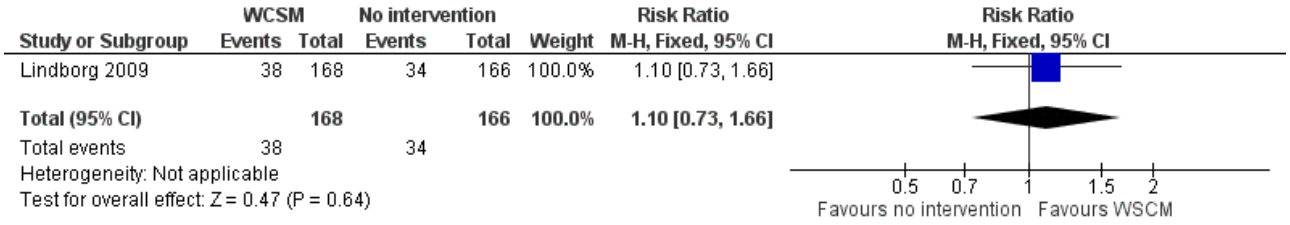
Only one study made this comparison (Lindborg 2009): women undergoing hysterosalpingo contrast sonography (HyCoSy) as a part of subfertility investigation were included.

Primary outcomes

2.1 Live birth

There was no evidence of a difference between the groups in live birth rates (OR 1.13, 95% CI 0.67 to 1.91, 1 RCT, 334 women). See Analysis 2.1; Figure 5.

Figure 5. Forest plot of comparison: 2 WSCM versus no intervention, outcome: 2.1 Live birth.



2.2 Ongoing pregnancy

There was no evidence of a difference between the groups in ongoing pregnancy rates (OR 1.14, 95% CI 0.71 to 1.84, 1 RCT, 334 women). See Analysis 1.2.

Sensitivity analyses

Use of risk ratios did not affect the findings for this comparison.

Secondary outcomes

2.3 Miscarriage

There was no evidence of a difference between the groups in miscarriage rates (OR 1.12, 95% CI 0.42 to 2.96, 1 RCT, 40 pregnancies). See Analysis 2.3.

2.4 Ectopic pregnancy

There was no evidence of a difference between the groups in ectopic pregnancy rates (OR 0.90, 95% CI 0.05 to 14.76, 1 RCT, 40 pregnancies). See Analysis 2.4.

2.5 Procedural pain, immediate and delayed

This outcome was not reported.

2.6 Short-term adverse events (intravasation, infection, haemorrhage)

There was one case of pelvic infection (n = 149) requiring treatment with intravenous antibiotics.

2.7 Image quality, of the uterine cavity and tubal ampulla

This outcome was not reported.

2.8 Long-term complications

This outcome was not reported.

(3) Tubal flushing with OSCM versus WSCM

Five studies made this comparison (Alper 1986; De Boer 1988; Lindequist 1994; Rasmussen 1991; Spring 2000).

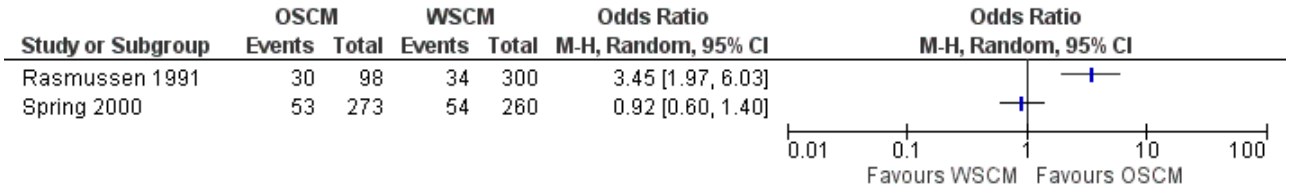
Primary outcomes

3.1 Live birth

Two studies reported this outcome (Rasmussen 1991; Spring 2000). They were not pooled due to extreme statistical heterogeneity (I^2 = 94%).

One of these studies (Rasmussen 1991) reported a higher live birth rate in the OSCM group (OR 3.45, 95% CI 1.97 to 6.03, 1 RCT, 398 women). The other found no difference between the groups (OR 0.92, 95% CI 0.60 to 1.40, 1 RCT, 533 women, random-effects model). No obvious explanation was found for this inconsistency in findings, although age differences at baseline in one of the studies (Spring 2000) may have favoured WSCM to some degree. See Analysis 3.1; Figure 6.

Figure 6. Forest plot of comparison: 3 OSCM versus WSCM, outcome: 3.1 Live birth.



3.2 Ongoing pregnancy

All five studies reported ongoing pregnancy. There was no evidence of a difference between the groups (OR 1.44, 95% CI 0.84 to 2.47, 5 RCTs, 1454 women, I^2 = 76%, random-effects model). The high heterogeneity was mainly due the effects of one study (Rasmussen 1991) that found a benefit for WSCM. Heterogeneity reduced to I^2 = 24% when this study was excluded from the analysis, and the overall finding of no difference between the groups did not change. See Analysis 3.2. No obvious reason for the heterogeneity was identified.

Subgroup analysis

All studies making this comparison were conducted primarily for diagnostic reasons.

Sensitivity analyses

None of the sensitivity analyses affected the findings for this comparison.

Secondary outcomes

3.3 Miscarriage

One study (Spring 2000) reported miscarriage. There was no evidence of a difference between the groups (OR 0.82 95% CI 0.40, 1.64, 1 RCT, 158 pregnancies). See Analysis 2.3.

3.4 Ectopic pregnancy

One study (Spring 2000) reported ectopic pregnancy. There was no evidence of a difference between the groups (OR 0.56, 95% CI 0.10 to 3.12, 1 RCT, 158 pregnancies). See Analysis 2.4.

3.5 Procedural pain, immediate and delayed

One study (Rasmussen 1991) reported the incidence of any postprocedural pain. Pain was less frequently reported in the OSCM group (OR 0.13, 95% CI 0.08 to 0.22, 1 RCT, 417 women). See Analysis 3.5.

A second study (Alper 1986) measured procedural pain 15 minutes after the intervention and found no difference between the groups on a scale of 0 to 5 (MD -0.30, 95% CI -0.78 to 0.18, 1 RCT, 106 women). See Analysis 3.6.

3.6 Short-term adverse events (intravasation, infection, haemorrhage)

The odds of the complication intravasation were higher with OSCM (OR 5.05, 95% CI 2.27 to 11.22, 3 RCTs, 768 women, I^2 = 0%) (De Boer 1988; Lindequist 1994; Rasmussen 1991).

There was no evidence of a difference between the groups in the odds of infection (OR 0.21, 95% CI 0.03 to 1.62, 2 RCTs, 662 women) or post-procedure bleeding (OR 0.65, 95% CI 0.40 to 1.06, 2 RCTS, 662 women, I^2 = 0%) (Lindequist 1994; Rasmussen 1991).

No serious complications were reported in these studies.

3.7 Image quality, of the uterine cavity and tubal ampulla

The odds of obtaining a satisfactory image were lower for OSCM than for WSCM, for both the uterine cavity (Peto OR 0.18, 95% CI 0.12 to 0.26) and the tubal ampulla (Peto OR 0.05, 95% CI 0.04 to 0.07) (De Boer 1988; Lindequist 1994; Rasmussen 1991).

3.8 Long-term complications

This outcome was not reported.

(4) Tubal flushing with OSCM + WSCM versus WSCM

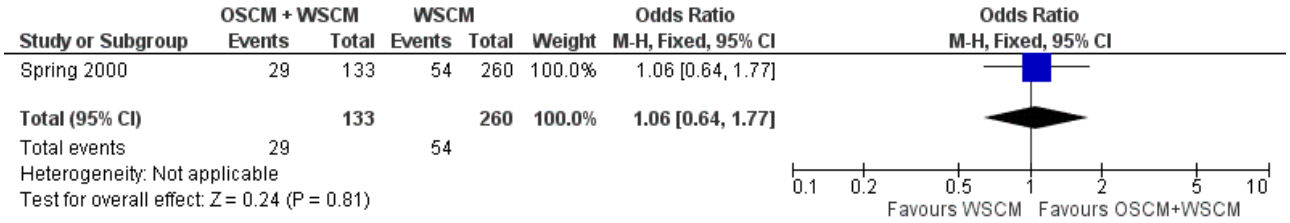
Four studies made this comparison (Al-Fadhli 2006; Spring 2000; Steiner 2003; Yang 1989).

Primary outcomes

4.1 Live birth

One study reported live birth (Spring 2000). There was no evidence of a difference between the groups (OR 1.06, 95% CI 0.64 to 1.77, 1 RCT, 393 women). See Analysis 4.1; Figure 7.

Figure 7. Forest plot of comparison: 4 OSCM + WSCM versus WSCM, outcome: 4.1 Live birth.



4.2 Ongoing pregnancy

Four studies reported ongoing pregnancy (Al-Fadhli 2006; Spring 2000; Steiner 2003; Yang 1989). There was no evidence of a difference between the groups (OR 1.23, 95% CI 0.87 to 1.72, 4 RCTs, 633 women, $I^2 = 0\%$). See Analysis 4.2.

Subgroup analysis

Findings did not differ substantially when the studies were subgrouped into therapeutic and diagnostic studies.

Sensitivity analyses

None of the sensitivity analyses affected the findings for this comparison.

Secondary outcomes

4.3 Miscarriage

There was no evidence of a difference between the groups in miscarriage rates (OR 1.14, 95% CI 0.53 to 2.48, 1 RCT, 393 women) (Spring 2000).

4.4 Ectopic pregnancy

There were no significant differences in ectopic pregnancy (OR 0.48, 95% CI 0.05 to 4.38, 2 RCTs, 422 women) (Letterie 1990; Spring 2000).

4.5 Procedural pain, immediate and delayed

This outcome was not reported.

4.6 Short-term adverse events (intravasation, infection, haemorrhage)

This outcome was not reported.

4.7 Image quality, of the uterine cavity and tubal ampulla

This outcome was not reported.

4.8 Long-term complications

This outcome was not reported.

Subgroup analysis

A subgroup analysis for whether the intervention was performed by HSG or laparoscopy did not significantly alter the outcome for either pregnancy rate after tubal flushing at laparoscopy (Peto OR 1.93, 95% CI 0.85 to 4.38) or hysterosalpingography (Peto OR 1.18, 95% CI 0.82 to 1.70).

DISCUSSION

Summary of main results

The results of this systematic review give some evidence that tubal flushing with OSCM increases the pregnancy rate compared no treatment. Our findings suggest that among women with a 17% chance of ongoing pregnancy if they have no intervention, the rate will increase to 29% to 35% if they have tubal flushing with OSCM. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power.

There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

The success rates of fertility treatments are best assessed in terms of live birth, and only 4 of the 13 studies included in this review assessed live birth as an outcome measure. Outcome measures should also include multiple pregnancy rates and treatment complications.

Overall completeness and applicability of evidence

The evidence was limited by small sample sizes for several comparisons, especially for the outcome of live birth. It is also not entirely clear which women are most likely to benefit from the intervention. The 24-month follow up of an RCT included in this meta-analysis (Johnson 2007) provided evidence of the effectiveness of lipiodol flushing for women with unexplained infertility. The initial trial showed a positive effect of lipiodol in women with mild endometriosis at six months follow up (Johnson 2004). The follow-up study showed no enhanced fertility beyond six months in women with endometriosis, but suggested a sustained and consistent enhanced fertility up to 24 months in women with pure unexplained infertility. However, another RCT suggests the most pronounced effect might be apparent in the subgroup of women with endometriosis who have normal patent fallopian tubes (Johnson 2004). Pregnancy rate and live birth were similar in the follow-up study (Brent 2006) of the first 100 women receiving lipiodol as a treatment.

Data on adverse events were scanty and in most cases unsuitable for pooling. There needs to be a proper evaluation of complications associated with these procedures.

Quality of the evidence

The overall quality of the evidence was low or very low for all comparisons. The main limitations were imprecision, risk of bias and heterogeneity. There were too few studies in any one comparison to evaluate the risk of publication bias. See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4.

The risk of bias in most of the primary studies was unclear or high for most domains, and only three described satisfactory methods of allocation concealment. Most were unblinded. As noted above, this may not have unduly influenced findings for live birth and pregnancy but could influence the assessment of adverse events. The possibility that increased sexual frequency in a non-blinded trial is a contributory factor to improved fertility is also a possible source for bias in unblinded trials. One trial (Johnson 2004) collected sexual frequency data and showed that there was no difference in subsequent sexual frequency for those randomised to tubal flushing compared to no treatment.

The source of funding was not stated in nine trials. In the remaining four trials, two were not industry supported (Lindborg 2009; Spring 2000) and in two studies it was stated only that products were supplied free of charge (Letterie 1990; Rasmussen 1991).

Potential biases in the review process

We are unaware of any potential biases in our review process.

Agreements and disagreements with other studies or reviews

Studies comparing OSCM with WSCM have shown a consistent and homogeneous therapeutic effect of oily media in previous meta-

analyses (Vandekerckhove 1993). Results from non-randomised studies have also suggested that OSCM tubal flushing increases pregnancy rates and that the pregnancy rate following OSCM tubal flushing exceeds that following WSCM tubal flushing (Watson 1994). The greatest effect of OSCM tubal flushing occurred in women with unexplained subfertility (Watson 1994).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence suggests that tubal flushing with oil-soluble contrast media may increase the chance of pregnancy and live birth compared to no intervention. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power. There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

Tubal flushing with oily media such as lipiodol could represent a simple, less invasive and cost-effective alternative to other modalities of treatment for couples where the woman has normal patent fallopian tubes. Moreover, it is less likely than other options to increase the risk of multiple pregnancy. We suggest that there is a strong argument for adopting this approach as a treatment for unexplained infertility. For safety reasons, we believe it is important for such procedures to be performed only under fluoroscopic control and in women with previously confirmed bilateral tubal patency.

Implications for research

Further robust randomised trials comparing oil-soluble versus water-soluble media or no treatment should be undertaken, with live birth as the primary outcome. Comparative data on adverse events should also be reported. Further scientific research on the OSCM-related improvement in fecundity may clarify its mechanism of working and explain some cases of hitherto 'unexplained' infertility. To investigate the potential advantages of flushing with OSCM a randomised controlled trial comparing this approach with IVF and intrauterine insemination for women with subfertility (either unexplained or with proven appropriately staged endometriosis) seems a logical next step. Future trials should take into account the timing and frequency of intercourse.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of these previous authors:

- Patrick Vandekerckhove was the primary author of the original review, was involved in trial selection and data extraction of trials for the updated review and critically reviewed the updated review in 2007
- Tasuku Harada and Richard Lilford were authors of the original review and commented on the updated review in 2007.

We would like to acknowledge members of the editorial office in Auckland for assistance with updates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Fadhli 2006

Methods	Method of randomisation: computer-generated random table Allocation concealment: not mentioned Blinding: not mentioned Analysis: power calculation suggested a requirement for 27 women per contrast group and 39 recruited per group Intention-to-treat analysis not performed but possible from the data Study setting: McGill University Health Center, Montreal, Quebec, Canada Duration of study: September 2002 to September 2004 Duration of follow up: 6 months Withdrawals: 88 women recruited and randomised 1 woman in the lipiodol group excluded (underwent an ovarian cystectomy during the same laparoscopy) 9 withdrawn after randomisation (4 lost to follow up and 5 had IVF immediately after the laparoscopy with dye sufflation) 78 women analysed Source of funding not stated
Participants	Number of participants: 88

Al-Fadhli 2006 *(Continued)*

	Mean age: 32 years (SD 0.6) WSCM; 31 years (SD 0.5) OSCM Inclusion criteria: infertile women, duration of infertility not mentioned Investigative work-up: early follicular FSH < 10 IU/L, normal semen analysis (criteria not mentioned), ovulatory confirmation by mid-luteal phase progesterone > 25 mmol/L, patent fallopian tubes at HSG. Included women had normal laparoscopic findings or stage I or II endometriosis Exclusion criteria: iodine allergy Breakdown by cause of infertility not specified Previous fertility treatments not specified
Interventions	Tubal flushing during laparoscopy, after sufflation with WSCM methylene blue dye: OSCM lipiodol (ultra-fluid; Guerbet/Ezem, Canada, Montreal, Quebec) versus WSCM saline A volume of 10 ml of contrast medium was used Timing not specified with menstrual cycle Co-interventions: excision of endometriosis during the laparoscopy was performed in 20 patients (11 WSCM + OSCM, 9 WSCM) Primarily intended as therapeutic procedure
Outcomes	Pregnancy rate (method of diagnosis not specified)
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mentions no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and losses to follow up totalled 11%
Selective reporting (reporting bias)	Unclear risk	Failed to report pain or adverse effects
Other bias	Low risk	No other potential bias identified

Alper 1986

Methods	Randomisation: random number table Allocation concealment: not mentioned Blinding: not mentioned

Alper 1986 *(Continued)*

	Trial design: parallel group Analysis: power calculation not mentioned. Intention-to-treat analysis not performed Study setting: single-centre; Ottowa Civic Hospital, Ottowa, Canada Duration of trial: 8 months Duration of follow up: 6 months Withdrawals:13 (9.9%) withdrawn after HSG; 12 (9.2%) lost to follow up 131 women recruited and randomised 106 women analysed
Participants	No of women: 106 analysed Mean age: mean age 29.3 years (SD 4.6) WSCM; 29.1 years (SD 2.9) OSCM Cause of infertility: Primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated, but duration and proportion of primary to secondary similar in two groups) Investigative work-up: semen analysis, PCT, BBT and endometrial biopsy; diagnostic laparoscopy prior to HSG in most women Breakdown specified by cause for infertility Previous fertility treatments not specified Women with bilateral tubal blockage withdrawn after HSG; no other exclusions specified
Interventions	HSG with OSCM ethiodol (Savage Laboratories, Missouri City, USA) versus WSCM Renographin (ER Squibb & Sons, Princeton, USA) A volume of 10 to 20 ml of contrast medium was used Timing: any day of menstrual cycle No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy (diagnosis based on urine hCG or serum beta-hCG plus ultrasound, all the patients had pregnancies confirmed by ultrasound) Volume of contrast medium used Pain during HSG Intravasation
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding in the text although this could have been possible
Blinding of outcome assessment (detection bias)	Unclear risk	No blinding mentioned for the outcome assessment

Alper 1986 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow up and withdrawals from the study totalled 19%
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	Low risk	No other potential bias identified

De Boer 1988

Methods	Randomisation: not stated Allocation concealment: not stated Blinding: not stated Analysis: not mentioned, intention-to-treat analysis not done Study setting: St Radboud University Hospital, Nijmegen, Holland Duration of trial: February 1985 to October 1986 Duration of follow up: 6 months Withdrawals: none
Participants	Number of participants: 175 Mean age: 29 years (19 to 44)Primary or secondary infertility for more than six months; mean infertility duration 37 (SD 26.2) months Investigative work-up: normal PCT or sperm penetration test, or both, and BBT Breakdown by cause for infertility: unexplained only Previous fertility treatments not specified other than exclusion for women with previous infertility surgery
Interventions	HSG with OSCM ethiodol (Guerbet, France) versus WSCM iopamidol (Bracco, Italy) A volume of 10 ml contrast medium was used Timing: day 6 to 13 of menstrual cycle No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy rate (diagnosis based on ultrasound, although ultrasound criteria not specified) Quality of visualisation of uterine cavity Quality of visualisation of ampullary tubal folds Time for contrast medium to disperse from pelvis
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not mentioned

De Boer 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Rates of loss to follow up and withdrawals from the study were unclear
Selective reporting (reporting bias)	Unclear risk	Failed to report pain or adverse effects
Other bias	Low risk	No other potential bias identified

Johnson 2004

Methods	Randomisation: two computer-generated random number sequences (A - women with unexplained infertility; B - women with endometriosis in the context of otherwise unexplained infertility) Allocation concealment: sequentially numbered sealed opaque envelopes Blinding: no blinding Trial design: parallel group Analysis: power calculation and intention-to-treat (ITT) analysis done Study setting: single-centre, University of Auckland Dept O & G with Fertility Plus, National Women's Hospital, Auckland, New Zealand Duration of trial: 3 years Duration of follow up: 6 months Withdrawals: none Two separate randomisation schedules were used for the endometriosis and unexplained infertility subpopulations Time of randomisation: on same cycle as HSG, usually several days before HSG Not blinded 158 women recruited and randomised No exclusions before HSG No withdrawals 2 protocol breaches 3 women lost to follow up 158 women analysed on ITT basis Duration of follow up: 6 months Single-centre: University of Auckland Dept O & G with Fertility Plus, National Women's Hospital, Auckland, New Zealand

Johnson 2004 *(Continued)*

Participants	No of women: 158 Mean age: 33.9 years (SD 2.9) for OSCM; 33.5 years (SD 3.8) for control Inclusion criteria: unexplained infertility (or endometriosis where fallopian tubes and ovaries unaffected by endometriotic disease) of duration > 12 months, full investigation for the cause complete, age 18 to 39 years, biochemistry as below; confirmed bilateral tubal patency Cause of infertility: unexplained primary or secondary infertility (primary 54.8% OSCM, 60.0% no treatment) for more than 12 months (mean duration of pre-existing infertility 54.8 months) Investigative work-up: normal semen analysis by WHO criteria, early follicular FSH < 10 IU/l, ovulatory confirmation by serum progesterone > 25 mmol/l, normal fallopian tubes at laparoscopy and dye insufflation or HSG Breakdown by cause for infertility: pure unexplained 61%, endometriosis with normal fallopian tubes and ovaries 39%, all other causes for infertility excluded Previous fertility treatments: IVF 34%, IUI 44%, empirical clomiphene 60%, women with endometriosis having previous surgical treatment 60%
Interventions	HSG with OSCM lipiodol versus no treatment Timed after menses but prior to Day 12 Information sheet on fertile phase of the cycle given to both groups; no other co-interventions Primarily intended as therapeutic procedure
Outcomes	Primary outcome: 1) clinical pregnancy (diagnosis based on positive pregnancy test and intrauterine gestation sac on ultrasound) 2) live birth Secondary outcome: 1) miscarriage 2) ectopic pregnancy 3) fetal death > 20 weeks 4) termination 5) multiple pregnancy 6) adverse events
Notes	Assigned treatment was clearly adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequences
Allocation concealment (selection bias)	Low risk	Allocation concealment: sequentially numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not possible to blind participants since the treatment involved HSG and control had no treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of executor of the assignment or the assessor at follow up

Johnson 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow up and withdrawals totalled 3%
Selective reporting (reporting bias)	Low risk	There is no indication that the study reported selected outcomes
Other bias	Low risk	No other potential bias identified

Letterie 1990

Methods	Randomisation: random number scheme Allocation concealment: no mention of this Blinding: no mention of this Trial design: parallel group Analysis: power calculation not mentioned; intention-to-treat analysis not feasible Study setting:Single-centre; Tripler Army Medical Centre, Honolulu, Hawaii, USA Duration of study: not mentioned Duration of follow up: 12 months Withdrawals: 11 withdrawn after randomisation (8 inadequate follow up and 3 "inadequate coital exposure")
Participants	No of patients: 29 Mean age: 27 (SD 3.5) years OSCM; 25 (SD 4.1) years WSCM (not significant) Cause of infertility: unexplained infertility of mean duration 24 (SD 14.5) months OSCM; 28 (SD 13.9) months WSCM; inclusion criterion > 12 months Inclusion criteria: ovulatory status as documented by biphasic basal body temperature with a 14-day luteal phase; serum progesterone > 3ng/ml or in phase secretory endometrium on biopsy, or both; normal semen analysis; normal pelvic anatomy and bilateral patent tubes Exclusion criteria: iodine allergy; evidence of endometriosis, tubal disease or pelvic adhesions Breakdown by cause: not done Investigative work-up: normal semen analysis; ovulatory confirmation based on BBT and serum progesterone or secretory phase, or both; normal prolactin, thyroxine and TSH; normal pelvis and bilateral tubal patency at laparoscopy Breakdown by cause for infertility: unexplained only Previous fertility treatments not specified Exclusions specified: where cause for infertility diagnosed; iodine allergy
Interventions	Tubal flushing during laparoscopy, after standard dye studies, with OSCM ethiodol (Savage Laboratories) versus WSCM Conray-60 (Mallinckrodt Inc.) A volume of 20 ml of contrast medium was used Timing not specified with menstrual cycle No co-interventions Primarily intended as therapeutic procedure
Outcomes	Pregnancy (diagnostic criteria not specified) Ectopic pregnancy

Letterie 1990 *(Continued)*

Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number scheme
Allocation concealment (selection bias)	Unclear risk	No mention in the paper
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of this in the paper
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow up and withdrawals totalled 28%
Selective reporting (reporting bias)	Unclear risk	Some aspects like how the pregnancy test was confirmed not clearly mentioned
Other bias	Low risk	No other potential bias identified

Lindborg 2009

Methods	Randomisation: computer-generated randomisation in blocks of 40 Allocation concealment: sealed opaque envelopes used Blinding: not done Analysis: intention-to-treat analysis done Trial design: parallel group Study setting: Reproductive unit at Sahlgrenska University, Gothenburg, Sweden Duration of study:December 2001 to May 2006 Duration of follow up: 6 months Withdrawals: clearly mentioned
Participants	Number of participants: 334 Mean age: 31.9 yrs Inclusions: at least 1 year of subfertility, already scheduled for HyCoSy Exclusions: > 40 yrs, severe male infertility, severe tubal pathology, suspected anovulation (menstrual period > 35 days)

Lindborg 2009 *(Continued)*

	Breakdown for cause: 63% primary infertility, mean duration of infertility 2.1 yrs
Interventions	All received transvaginal scan prior to use of contrast medium (hydrosalpinx contraindication) Saline injected into uterine cavity to achieve distension, WSCM (Echovist, Bayer AG) instilled to evaluate tubal patency Maxiumum 15 ml used Categorical statement made for each tube (patent, occluded, unclear) All received oral antibiotic postprocedure Timing not specified with menstrual cycle No co-interventions
Outcomes	Primary outcome clinically pregnancy defined sonographically as visible fetal sac within 6 months Live birth Miscarriage Ectopic pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Physicians aware of allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow up and withdrawals totalled 22%
Selective reporting (reporting bias)	Low risk	There is no indication that the study has reported selected outcomes
Other bias	Low risk	No other potential bias identified

Lindequist 1994

Methods	Method of randomisation: not stated

Lindequist 1994 *(Continued)*

	Allocation concealment: not mentioned Blinding: not mentioned Analysis: no mention of power calculation, intention-to-treat analysis not performed nor possible Study design: parallel group Study setting: Odense University Hospital, Odense, Denmark Duration of study: September 1989 to April 1991 Duration of follow up: 20 to 39 months Withdrawals: 307 recruited and randomised, 60 patients excluded prior to HSG or lost to follow up, 5 withdrawn after HSG
Participants	No of participants: 242 Mean age: 29.9 yrs OSCM (21 t0 43); 29.5 yrs WSCM (20 to 40) Inclusions: primary or secondary infertility for more than 12 months; secondary 48 (40%) OSCM, 42 (35%) WSCM Exclusion criteria: pregnant prior to HSG; HSG declined; technical difficulties leading to unsuccessful HSG; HSG not performed by authors; infertility < 12 months Mean duration of pre-existing infertility 41 months OSCM, 40 months WSCM Breakdown by cause for infertility not specified Previous fertility treatments not specified
Interventions	HSG with OSCM lipiodol (Laboratories Guerbet, France) versus HSG with WSCM Iotrolan A volume of 5 to 10 ml of contrast medium was used Timed between end of menses and Day 10 No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy (method of diagnosis not specified, but data extracted from Danish Patient Database to complete information with respect to pregnancy) Image quality Pain Infection Haemorrhage
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned

Lindequist 1994 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	All examinations and evaluations performed by authors
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow up and withdrawals totalled 21%
Selective reporting (reporting bias)	Low risk	Pregnancy information from Danish database
Other bias	Low risk	No other potential bias identified

Nugent 2002

Methods	Method of randomisation: third party sealed envelopes with allocation inside Allocation concealment: adequate Blinding: not blinded Analysis: power calculation specified a requirement for 180 recruits but trial terminated early owing to slow recruitment rate and running out of time Intention-to-treat analysis performed Study setting: Leeds General Infirmary and Princess Royal Hospital, Hull, UK Duration of study: 10 months Duration of follow up: 6 months Withdrawals: nil
Participants	Number of participants: 34 Mean age: 30.6 years (eligibility criterion < 36 years). Inclusion criteria: unexplained primary or secondary infertility (proportion of primary and secondary not stated) for more than 12 months (mean duration of pre-existing infertility 49 months) Investigative work-up: normal semen analysis by WHO criteria, ovulatory confirmation by serum progesterone or serial scanning, normal fallopian tubes at laparoscopy and dye insufflation or HSG Breakdown by cause for infertility: unexplained only, all other causes for infertility excluded Previous fertility treatments not specified
Interventions	HSG with OSCM lipiodol versus no treatment Timing with menstrual cycle not specified Information sheet on fertile phase of the cycle given to both groups; no other co-interventions Primarily intended as therapeutic procedure
Outcomes	Pregnancy rate (diagnosis based on positive pregnancy test) Viable pregnancy (diagnosis based on fetal heart on ultrasound) Adverse events
Notes	Assigned treatment was clearly adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement

Nugent 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Third party sealed envelope entry
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants apparently included in analysis
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	Low risk	No other potential bias identified

Ogata 1993

Methods	Method of randomisation: not stated Allocation concealment: Blinding: not mentioned Analysis: no mention of power calculation. Intention-to-treat analysis not done nor possible Study setting: University of Kyusyu, Fukuoka, Japan Study duration: November 1989 to February 1991 Duration of follow up: 4 months Withdrawals: ? exclusions after randomisation before HSG ? withdrawals after HSG: only women who had 4 ovulatory cycles were analysed ? losses to follow up
Participants	Number of participants: 302 randomised (148 versus 154). Those who failed to complete the four ovulatory cycles of observation were excluded, so only 190 were included in analysis (105 versus 85) Mean age: not specified; said to be similar between the 2 groups Inclusion criteria: primary or secondary infertility (proportion not specified) having first visit to infertility clinic; duration of infertility not specified but said to be similar between the 2 groups Investigative work-up: not specified, but rate of male infertility and PCT results said to be similar between the 2 groups Breakdown by cause for infertility not specified Previous fertility treatments not specified No exclusion criteria specified
Interventions	HSG with oil-soluble contrast medium lipiodol (Ultra-Fluid) versus no HSG (the HSG was delayed for 4 months until after the analysis)

Ogata 1993 *(Continued)*

	Volume of contrast medium not specified Timing with respect to menstrual cycle not specified No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy (method of diagnosis not specified)
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention of randomisation process
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow up and withdrawals totalled 37% (102/302)
Selective reporting (reporting bias)	Unclear risk	Failed to report pain or adverse effects
Other bias	Low risk	No other potential bias identified

Rasmussen 1991

Methods	Method of randomisation: not stated Allocation concealment: not stated Blinding: no mention Analysis: intention-to-treat analysis not done or not possible, no mention of power calculation Study setting: Odense University Hospital, Odense, Denmark Duration of study: 1985 to 1988 Duration of follow up: 9 months Withdrawals: 507 recruited and randomised, 78 excluded prior to HSG, 31 withdrawn after HSG, 14 lost to follow up (out of 207 in total)
Participants	Number of participants: 398

Rasmussen 1991 *(Continued)*

	Mean age: not stated Inclusion: primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated) Exclusion criteria: pregnant prior to HSG; HSG declined; technical difficulties leading to unsuccessful HSG; HSG not performed by authors Investigative work-up: not stated Breakdown by cause for infertility not specified Previous fertility treatments not specified
Interventions	HSG with OSCM lipiodol (Laboratories Guerbet, France) versus 3 types of WSCM: iohexol (Omnipaque 350, Nycomed, Oslo), Ioxaglate (Hexabrix 320, Laboratoire Guerbet, France), diatrizoate (Urografin, Schering, Berlin). As there were no outcome differences between the 3 groups using WSCM, they were combined in the analysis of results A volume of 5 to 10 ml of contrast medium was used Timing with menstrual cycle not specified No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy (method of diagnosis not specified) Other outcomes of this trial (reported image quality, pain, infection, haemorrhage and intravasation) are reported in a separate publication (Lindequist 1991)
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention to suggest this
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow up and withdrawals totalled 9%
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	Low risk	No other potential bias identified

Spring 2000

Methods	Method of randomisation: computer-generated random numbers in blocks of 9 at each site

Spring 2000 *(Continued)*

	Allocation concealment: adequate Blinding: not mentioned Analysis: power calculation suggested a requirement for 257 women per contrast group (achieved for 2 groups and recruitment abandoned for third group owing to difficulty recruiting) Intention-to-treat analysis not performed Study setting: 10 centres co-ordinated by the Kaiser Permanente Medical Care Program Infertility Work Group, California, USA Duration of study: December 1993 to July 1996 Duration of follow up: 12 months Withdrawals: 673 recruited and randomised, 7 lost to follow-up
Participants	Number of participants: 666 Mean age: 29.3 yrs (SD 4.6) years WSCM; 29.1 yrs (SD 2.9) years OSCM Inclusion criteria: primary or secondary infertility (OSCM 35.0%, WSCM 37.1%, WSCM + OSCM 34.8% primary infertility). Mean duration of infertility: OSCM 3.13 (SD 3.03) years, WSCM 3.15 (SD 3.18) years, WSCM + OSCM 3.09 (SD 3.61); eligibility criterion > 12 months Investigative work-up: not specified Breakdown by cause for infertility not specified Previous fertility treatments not specified Exclusion criteria: nil
Interventions	HSG with OSCM ethiodol (Savage Laboratories, Melville, USA) versus WSCM diatrizoate and iodipamide (Bracco Diagnostics, New Brunswick, USA) versus both WSCM and OSCM Volume WSCM mean 9.4 (range 2 to 75) ml; OSCM mean 8.6 (range 1 to -55) ml; both - WSCM mean 8.2 (range 1 to 30) ml and OSCM mean 6.0 (range 1 to 20) ml Timing with menstrual cycle not specified Co-interventions: artificial insemination performed in 25.3% OSCM; 24.6% WSCM; 24.8% WSCM + OSCM Primarily intended as diagnostic procedure
Outcomes	Pregnancy (diagnostic criteria not specified) Live birth Miscarriage Ectopic pregnancy
Notes	Assigned treatment was clearly adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number scheme
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Same clinician provided patient details, carried out HSG and reported the results

Spring 2000 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow up and withdrawals totalled 1%
Selective reporting (reporting bias)	Low risk	No selective reporting identified
Other bias	High risk	Interventions not delivered as planned: 25/133 women randomised to receive both WCSM and OSCM did not receive OSCM due to tubal abnormalities shown on WSCM Groups unequal at baseline: younger women (aged 20 to 24) more likely to be assigned to WSCM, women aged 35 to 39 more likely to be assigend to OSCM

Steiner 2003

Methods	Method of randomisation: computer-generated random numbers Allocation concealment: not concealed Analysis: no power calculation, intention to treat analysis not done Blinding: not done Study setting: University of Carolina, USA Duration of study: August 1996 to November 2000 Duration of follow up: 18 months Withdrawals: 698 recruited, 642 excluded, 3 lost to follow up
Participants	Number of participants: 56 Mean age: 32.9 (SD 3.4) years WSCM; 32.6 (SD 3.6) years WSCM + OSCM Inclusion criteria: primary or secondary infertility (WSCM 57.5%, WSCM + OSCM 46.7% primary infertility) Mean duration of infertility: WSCM 2.9 (SD 3.0) years, WSCM + OSCM 2.8 (SD 2.3) years; eligibility criterion > 12 months Exclusion criteria: iodine allergy, non-patent tubes, refusal to participate Investigative work-up: not specified Breakdown by cause for infertility specified but data for subpopulations could not be extracted Previous fertility treatments not specified
Interventions	HSG with WSCM Sinografin (Bracco Diagnostics, New Brunswick, USA) versus WSCM Sinografin + OSCM ethiodol (Savage Laboratories, Melville, USA) Timing with menstrual cycle not specified Co-interventions: ovulatory medication used in 61.5% WSCM; 53.3% WSCM + OSCM Primarily intended as therapeutic procedure
Outcomes	Pregnancy (self report or positive blood or urine pregnancy test) Time to conception
Notes	Allocation was not concealed from physicians; patients were informed of allocation after randomisation before treatment

Steiner 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number scheme
Allocation concealment (selection bias)	Unclear risk	No allocation concealment done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinicians reporting the outcome were aware of the allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow up and withdrawals totalled 5%
Selective reporting (reporting bias)	Unclear risk	Failed to report pain or adverse effects
Other bias	Low risk	No other potential bias identified

Yang 1989

Methods	Method of randomisation: not stated. Allocation concealment: unclear Blinding: double blind Analysis: no mention of power calculation, intention-to-treat analysis not done Study setting: Mackay Memorial Hospital, Taipei, Japan Duration of study: October 1986 to March 1987 Duration of follow up: 8 months Withdrawals: nil
Participants	Number of participants: 109 Participant age: range 22 to 44 years; mean age WSCM 30.1 years, WSCM + OSCM 30.0 years Inclusion criteria: primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated) Exclusion criteria: not mentioned Investigative work-up: not stated Breakdown specified by cause for infertility Previous fertility treatments not specified
Interventions	HSG with WSCM Telebrix Hystero (Laboratories Guerbet) versus WSCM Telebrix Htstero followed by OSCM lipiodol Ultrafluide (Laboratories Guerbet)

Yang 1989 *(Continued)*

	A volume of 10 ml WSCM and 5 ml OSCM were used Timing with menstrual cycle not specified No co-interventions Primarily intended as diagnostic procedure
Outcomes	Pregnancy (method of diagnosis not specified)
Notes	Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States it is double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Failed to report pain or adverse effects
Other bias	Low risk	No other potential bias identified

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acton 1988	Non-randomised study comparing HSG with OSCM versus WSCM in 420 women
Barwin 1971	Non-randomised study comparing HSG with OSCM versus WSCM in 248 women
Court 2014	Non-randomised observational study looking at pregnancy rates in 100 patients undergoing HSG using OSCM
DeCherney 1980	Non-randomised study comparing HSG with OSCM versus WSCM in 339 women
Gillespie 1965	Non-randomised study comparing HSG with OSCM versus WSCM in 271 women
Mackey 1971	Non-randomised study of HSG with OSCM versus WSCM versus no treatment in 523 women. (Showed no therapeutic effect of HSG with WSCM (OR 0.87, 95% CI 0.47 to 1.59), but a significantly higher pregnancy rate after HSG with OSCM (OR 1.60, 95%CI 1.09 to 2.35))

Study	Reason for exclusion
Perquin 2006	Randomised controlled trial comparing hysterosalpingography prior to laparoscopy and dye in 344 women
Schwabe 1983	Described as 'pseudo-randomised' with alternate assignment (thus not a truly randomised trial and therefore excluded), studied HSG with OSCM versus WSCM in 198 women (121 analysed). (Showed no significant difference in the odds of pregnancy for OSCM versus WSCM (OR 2.00, 95% CI 0.74 to 5.45))
Wolf 1989	Double-blind RCT of HSG with Iotrolan (WSCM) versus Iohexol versus diatrizoate assessing image quality and pain, but not pregnancy outcomes, in 60 women. A potential therapeutic effect on subsequent pregnancy outcomes could not therefore be studied
Yaegashi 1987	Non-randomised study of HSG with OSCM versus WSCM in 224 women. The details of this study were confirmed after commissioning a translation from the original Japanese publication

Characteristics of ongoing studies *[ordered by study ID]*

Dreyer 2014

Trial name or title	H2Olie study
Methods	Randomised single-blind parallel trial comparing oil-based contrast medium with water-based contrast medium for tubal flushing
Participants	Inclusion 1. Age between 18 up to and including 39 years 2. Subfertility of at least one year 3. Chlamydia antibody titer (CAT) negative 4. Low risk of tubal pathology according to the medical history 5. Valid indication for HSG in the fertility work-up or before intrauterine insemination treatment Exclusions 1. Endocrino-pathological diseases as: PCOS, Cushing syndrome, adrenal hyperplasia, hyperprolactinemia, acromegaly, hypothalamic amenorrhea, hypothyroidy, diabetes mellitus type 1 2. Known or high risk for tubal pathology, CAT positive 3. Known contrast (iodine) allergy 4. Male subfertility defined as a post-wash total motile sperm count < 3 x 10^6 spermatozoa/ml 5. If not willing or able to sign the consent form
Interventions	Tubal flushing with oil-based contrast medium versus water-based contrast medium
Outcomes	Primary: ongoing pregnancy rates Secondary: live birth rates, miscarriages, ectopic pregnancy and pain scores
Starting date	1/12/2011
Contact information	K Dreyer: k.dreyer@vumc.nl,

Dreyer 2014 *(Continued)*

	Department of Reproductive Medicine VU University Medical Center PK 6Z K180 De Boelelaan 1118, 1081 HV, Amsterdam, The Netherlands, +31 (0)20 4445277
Notes	Data collection complete at November 2014; results expected at ESHRE 2015 Funding: VU University Medical Center NTR3270 accessed 25/11/2014

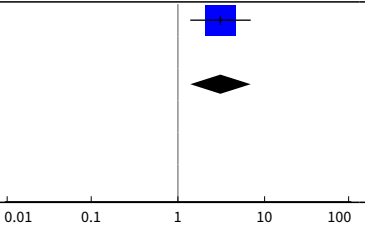
DATA AND ANALYSES

Comparison 1. OSCM versus no intervention

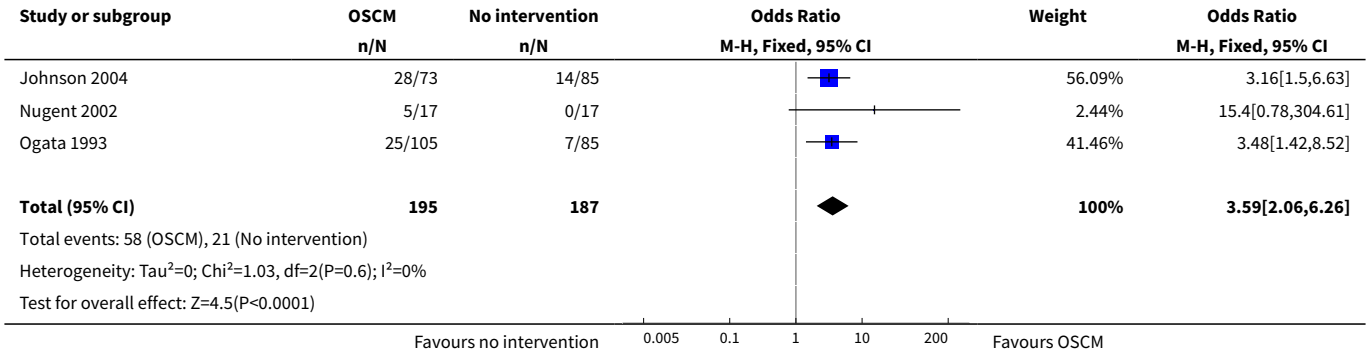
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	158	Odds Ratio (M-H, Fixed, 95% CI)	3.09 [1.39, 6.91]
2 Ongoing Pregnancy	3	382	Odds Ratio (M-H, Fixed, 95% CI)	3.59 [2.06, 6.26]
3 Miscarriage per pregnancy	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.25]
4 Procedural pain	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Ectopic pregnancy per pregnancy	1	42	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.06, 41.34]
6 Intravasation	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Infection	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Haemorrhage	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Long term complications	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 OSCM versus no intervention, Outcome 1 Live birth.

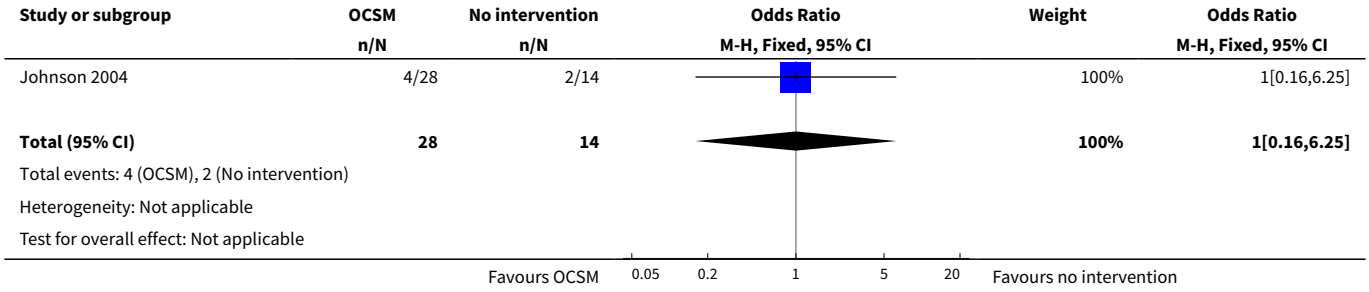
Study or subgroup	OSCM n/N	No intervention n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Johnson 2004	23/73	11/85		100%	3.09[1.39,6.91]
Total (95% CI)	**73**	**85**		**100%**	**3.09[1.39,6.91]**
Total events: 23 (OSCM), 11 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					



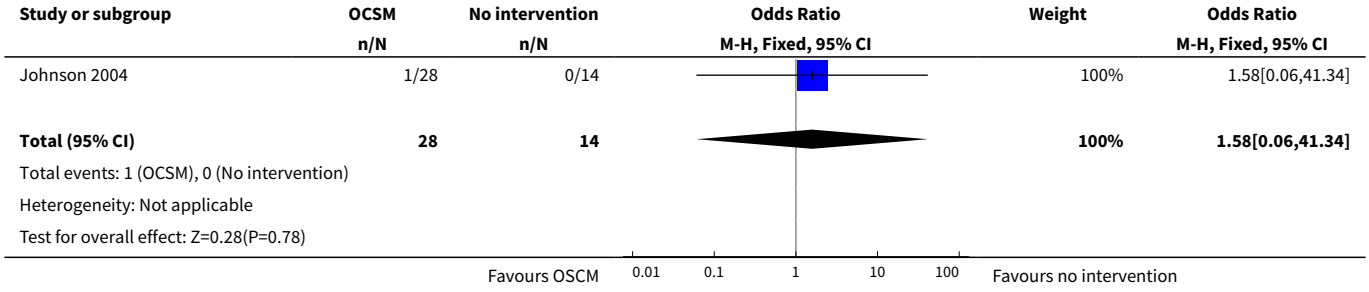
Analysis 1.2. Comparison 1 OSCM versus no intervention, Outcome 2 Ongoing Pregnancy.



Analysis 1.3. Comparison 1 OSCM versus no intervention, Outcome 3 Miscarriage per pregnancy.



Analysis 1.5. Comparison 1 OSCM versus no intervention, Outcome 5 Ectopic pregnancy per pregnancy.

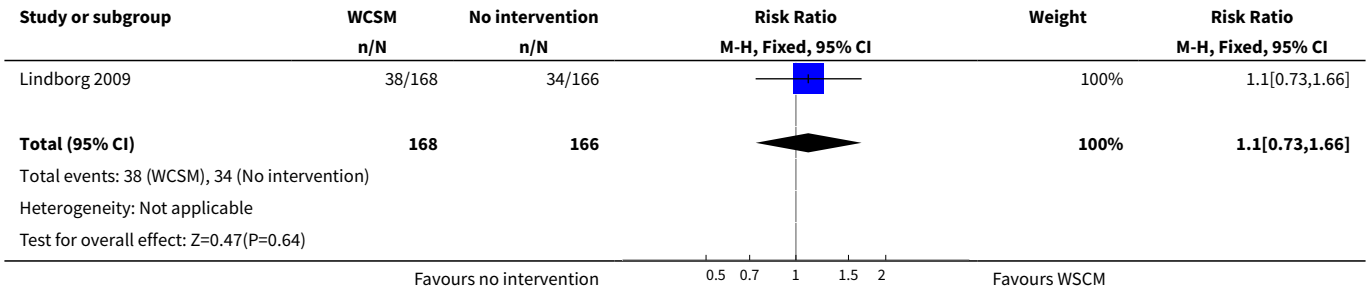


Comparison 2. WSCM versus no intervention

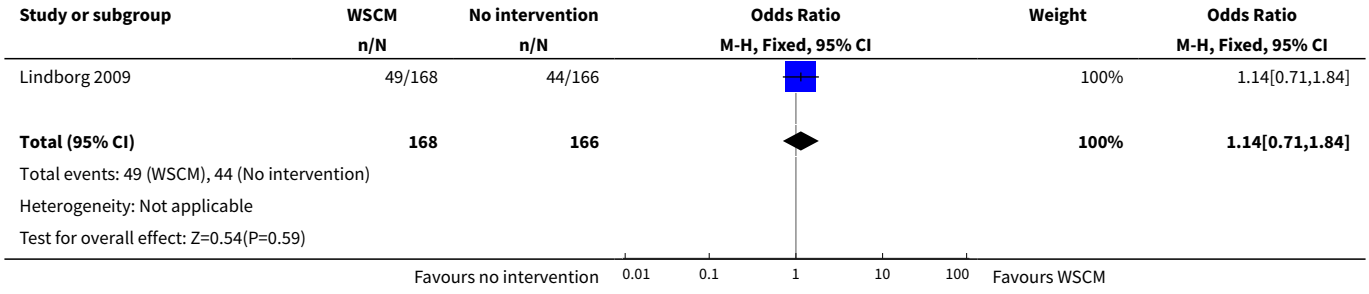
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Live birth	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.73, 1.66]
2 Ongoing Pregnancy	1	334	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.71, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Miscarriage per pregnancy	1	93	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.35, 2.90]
4 Ectopic pregnancy	1	93	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.05, 14.76]
5 Procedural pain	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Intravasation	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Infection	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Haemorrhage	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Long term complications	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

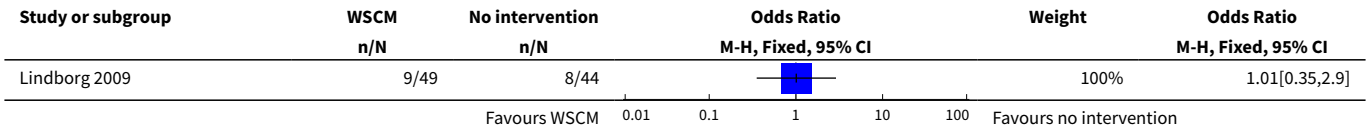
Analysis 2.1. Comparison 2 WSCM versus no intervention, Outcome 1 Live birth.

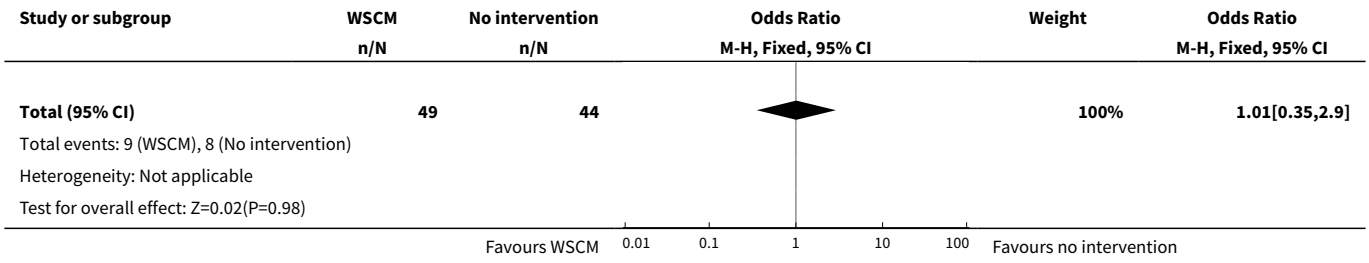


Analysis 2.2. Comparison 2 WSCM versus no intervention, Outcome 2 Ongoing Pregnancy.

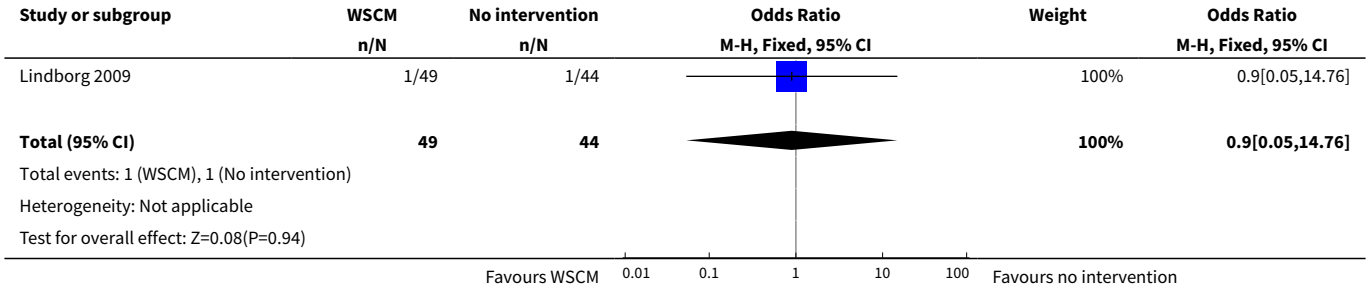


Analysis 2.3. Comparison 2 WSCM versus no intervention, Outcome 3 Miscarriage per pregnancy.





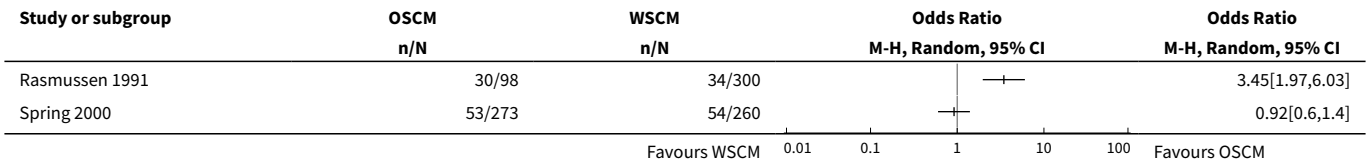
Analysis 2.4. Comparison 2 WSCM versus no intervention, Outcome 4 Ectopic pregnancy.



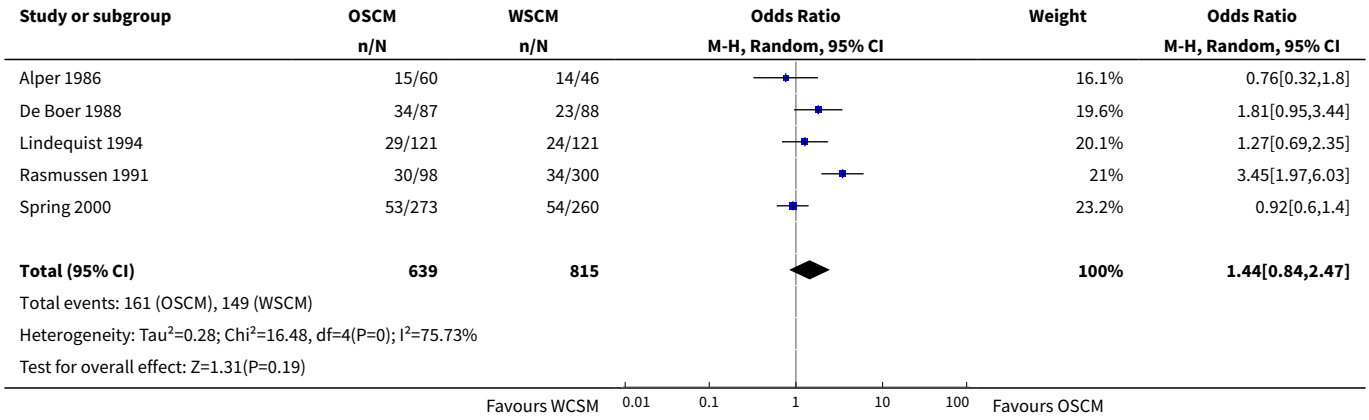
Comparison 3. OSCM versus WSCM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ongoing pregnancy	5	1454	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.84, 2.47]
3 Miscarriage per pregnancy	1	158	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.40, 1.64]
4 Ectopic pregnancy	1	158	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.10, 3.12]
5 Any postprocedural pain (dichotomous variable)	1	417	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.08, 0.22]
6 Procedural pain (continuous variable)	1	106	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.78, 0.18]
7 Intravasation	3	768	Odds Ratio (M-H, Fixed, 95% CI)	5.05 [2.27, 11.22]
8 Infection	2	662	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.62]
9 Haemorrhage	2	662	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.40, 1.06]
10 Long term complications	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

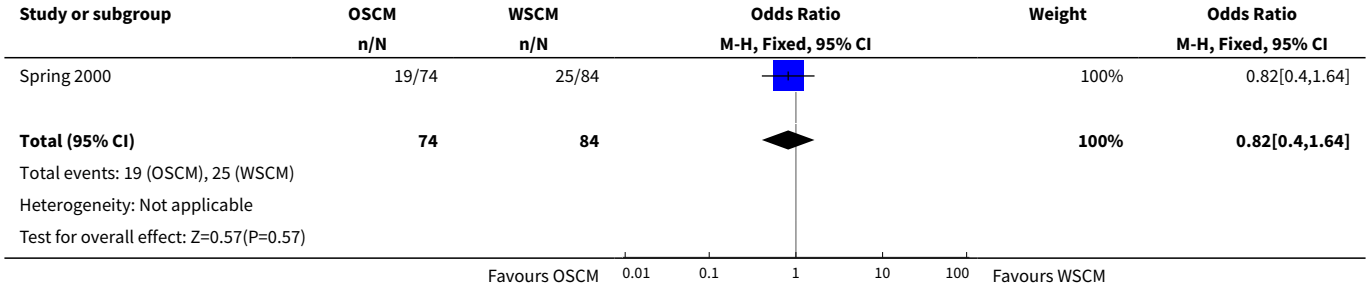
Analysis 3.1. Comparison 3 OSCM versus WSCM, Outcome 1 Live birth.



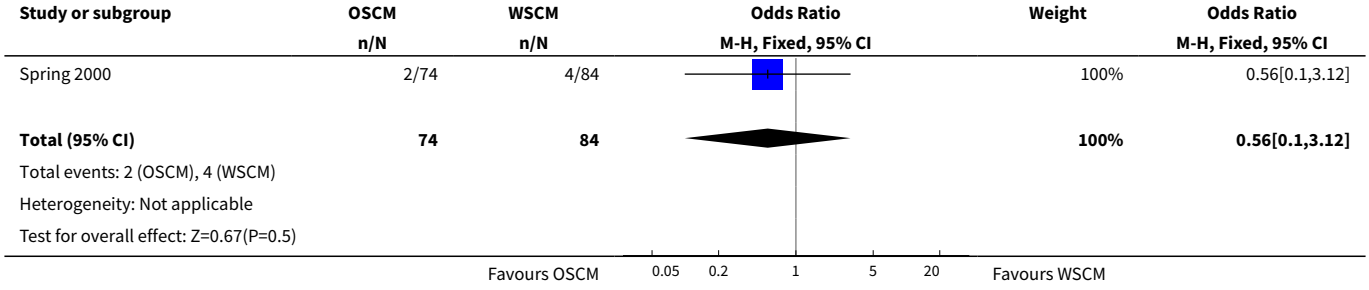
Analysis 3.2. Comparison 3 OSCM versus WSCM, Outcome 2 Ongoing pregnancy.



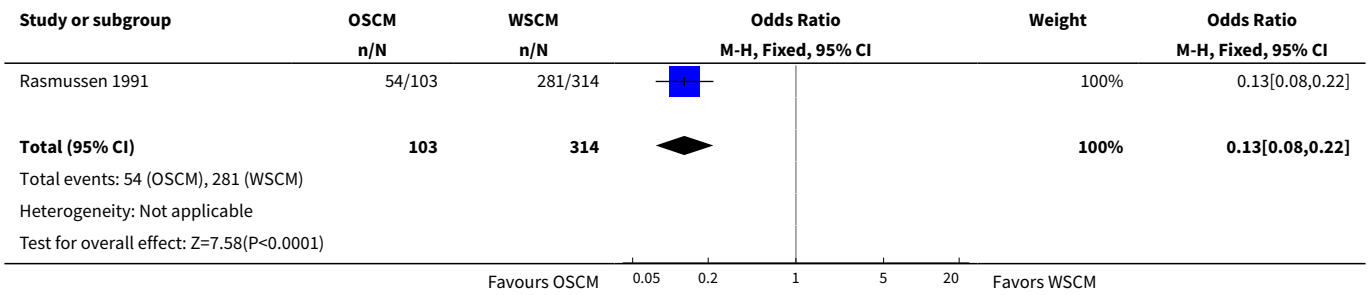
Analysis 3.3. Comparison 3 OSCM versus WSCM, Outcome 3 Miscarriage per pregnancy.



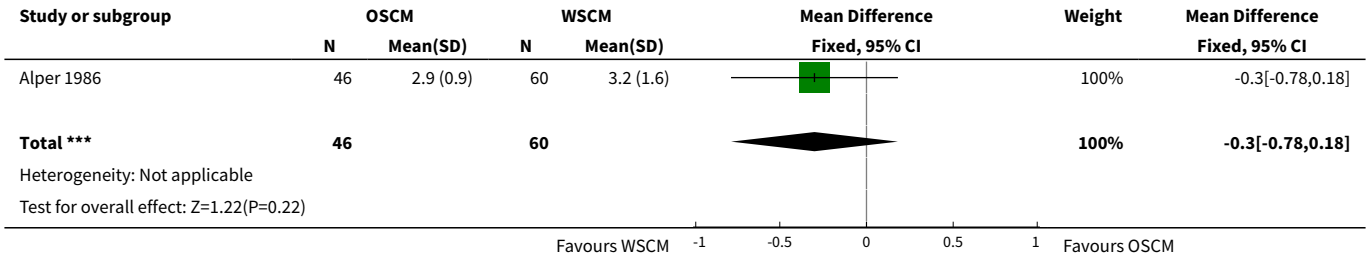
Analysis 3.4. Comparison 3 OSCM versus WSCM, Outcome 4 Ectopic pregnancy.



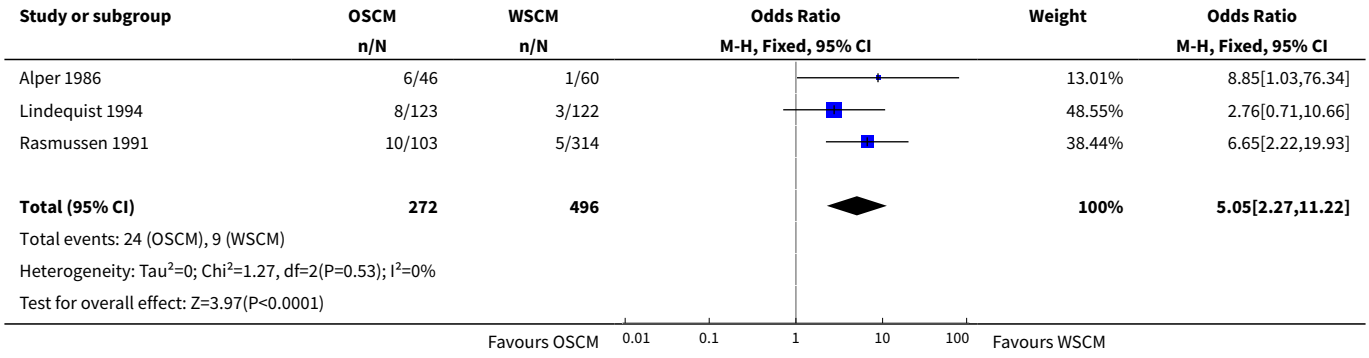
Analysis 3.5. Comparison 3 OSCM versus WSCM, Outcome 5 Any postprocedural pain (dichotomous variable).



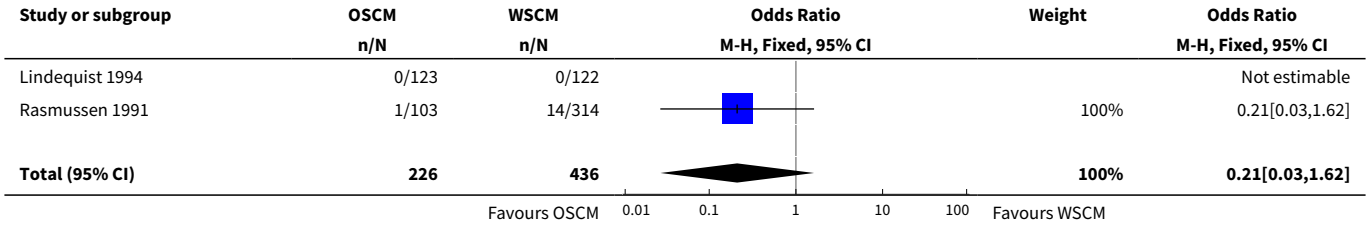
Analysis 3.6. Comparison 3 OSCM versus WSCM, Outcome 6 Procedural pain (continuous variable).

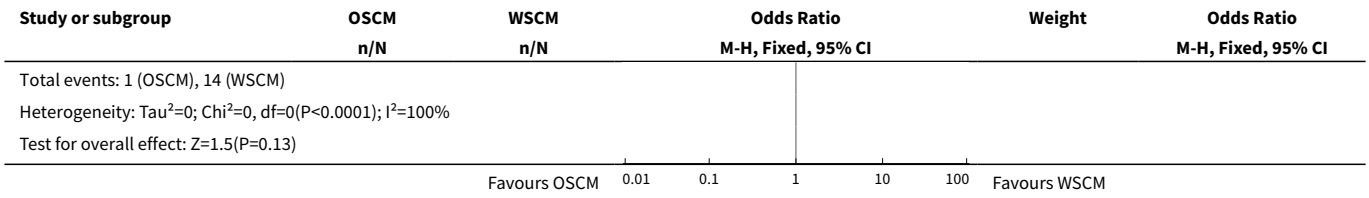


Analysis 3.7. Comparison 3 OSCM versus WSCM, Outcome 7 Intravasation.

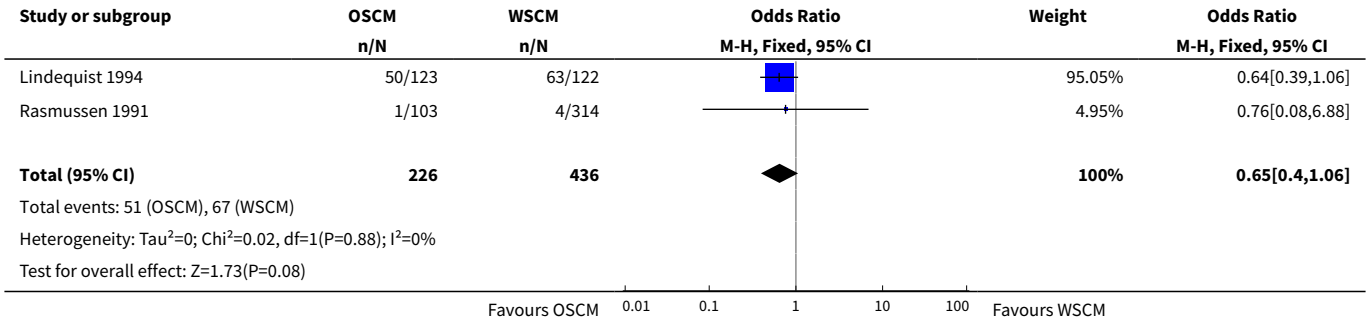


Analysis 3.8. Comparison 3 OSCM versus WSCM, Outcome 8 Infection.





Analysis 3.9. Comparison 3 OSCM versus WSCM, Outcome 9 Haemorrhage.



Comparison 4. OSCM + WSCM versus WSCM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	393	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.64, 1.77]
2 Ongoing Pregnancy	4	633	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.87, 1.72]
3 Miscarriage per pregnancy	1	130	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.53, 2.48]
4 Ectopic pregnancy	2	422	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 4.38]
5 Procedural pain	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Intravasation	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Infection	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Haemorrhage	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Long term complications	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

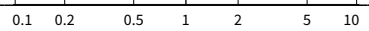
Analysis 4.1. Comparison 4 OSCM + WSCM versus WSCM, Outcome 1 Live birth.

Study or subgroup	OSCM + WSCM n/N	WSCM n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Spring 2000	29/133	54/260		100%	1.06[0.64,1.77]
Total (95% CI)	**133**	**260**		**100%**	**1.06[0.64,1.77]**
Total events: 29 (OSCM + WSCM), 54 (WSCM)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					

Favours WSCM — Favours OSCM+WSCM

Analysis 4.2. Comparison 4 OSCM + WSCM versus WSCM, Outcome 2 Ongoing Pregnancy.

Study or subgroup	OSCM + WSCM n/N	WSCM n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Al-Fadhli 2006	16/39	12/39		11.79%	1.57[0.62,3.98]
Spring 2000	46/133	84/260		61.97%	1.11[0.71,1.72]
Steiner 2003	18/28	14/25		8.8%	1.41[0.47,4.27]
Yang 1989	18/48	19/61		17.43%	1.33[0.6,2.94]
Total (95% CI)	**248**	**385**		**100%**	**1.23[0.87,1.72]**
Total events: 98 (OSCM + WSCM), 129 (WSCM)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=3(P=0.9); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					



Favours WSCM — Favours OSCM+WSCM

Analysis 4.3. Comparison 4 OSCM + WSCM versus WSCM, Outcome 3 Miscarriage per pregnancy.

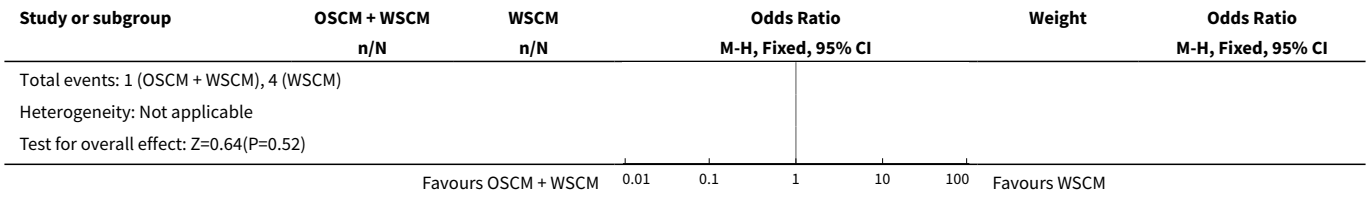
Study or subgroup	OSCM + WSCM n/N	WSCM n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Spring 2000	15/46	25/84		100%	1.14[0.53,2.48]
Total (95% CI)	**46**	**84**		**100%**	**1.14[0.53,2.48]**
Total events: 15 (OSCM + WSCM), 25 (WSCM)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.34(P=0.74)					

Favours OSCM + WSCM — Favours WSCM

Analysis 4.4. Comparison 4 OSCM + WSCM versus WSCM, Outcome 4 Ectopic pregnancy.

Study or subgroup	OSCM + WSCM n/N	WSCM n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Letterie 1990	0/15	0/14			Not estimable
Spring 2000	1/133	4/260		100%	0.48[0.05,4.38]
Total (95% CI)	**148**	**274**		**100%**	**0.48[0.05,4.38]**

Favours OSCM + WSCM — Favours WSCM



APPENDICES

Appendix 1. MDSG search strategy

Menstrual Disorders and Subfertility database search strategy for NJ212 11.01.11- limited to 2007 until present.

Keywords CONTAINS "fertility" or "subfertility" or "infertility" or "hysterosalpingogram" or "hysterosalpingography" or "laparoscopic chromopertubation" or "laparoscopy" or "Fallopian-Tube-Patency-Tests" or "tubal flushing" or "tubal patency" or "flushing media" or Title CONTAINS "fertility" or "subfertility" or "infertility" or "hysterosalpingogram" or "hysterosalpingography" or "laparoscopic chromopertubation" or "laparoscopy" or "Fallopian-Tube-Patency-Tests" or "tubal flushing" or "tubal patency" or "flushing media"

AND

Keywords CONTAINS "oil" or "oil-soluble contrast" or "Water-Soluble Contrast" or "Aqueous" or "lipiodol" or "lipiodol flushing" or "lipiodol-pingyangmycin emulsion" or "Contrast-Media" or "Flushing" or Title CONTAINS "oil" or "oil-soluble contrast" or "Water-Soluble Contrast" or "Aqueous" or "lipiodol" or "lipiodol flushing" or "lipiodol-pingyangmycin emulsion" or "Contrast-Media" or "Flushing"

Appendix 2. MEDLINE search strategy

1 HYSTEROSALPINGOGRAPHY/ or hysterosalpingog$.tw. (4547)
2 salpingog$.tw. (181)
3 HSG.tw. (1046)
4 laparoscop$.tw. (82655)
5 LAPAROSCOPY/ (59726)
6 Fallopian Tube Patency Tests/ (601)
7 (tubal adj flush$).tw. (23)
8 (tub$ adj patency).tw. (833)
9 chromopertub$.tw. (99)
10 fertili$.tw. (105699)
11 or/1-10 (199539)
12 OILS/ (9645)
13 oil$.tw. (97949)
14 Ethiodized Oil/ (529)
15 ethiodol.tw. (119)
16 iotrolan.tw. (199)
17 poppy.tw. (766)
18 Iodized Oil/ (2894)
19 IODIPAMIDE/ (620)
20 WATER/ (111567)
21 Contrast Media/ (65942)
22 contrast medi$.tw. (20603)
23 (water adj soluble).tw. (31267)
24 (oil adj soluble).tw. (339)
25 aqueous.tw. (131938)
26 lipiodol.tw. (2225)
27 OSCM.tw. (12)
28 WSCM.tw. (15)
29 or/12-28 (419392)
30 11 and 29 (3180)
31 randomized controlled trial.pt. (376220)
32 controlled clinical trial.pt. (88548)
33 randomized.ab. (296250)

34 placebo.tw. (159087)
35 clinical trials as topic.sh. (170403)
36 randomly.ab. (214362)
37 trial.ti. (127538)
38 (crossover or cross-over or cross over).tw. (60957)
39 or/31-38 (929229)
40 exp animals/ not humans.sh. (3951224)
41 39 not 40 (856083)
42 30 and 41 (133)
43 (201308$ or 201309$ or 201310$ or 201311$ or 201312$).ed. (411662)
44 2014$.ed. (453961)
45 2014$.dp. (442079)
46 43 or 44 or 45 (1207235)
47 42 and 46 (9)

Appendix 3. EMBASE search strategy

1 exp HYSTEROSALPINGOGRAPHY/ (4376)
2 hysterosalpingog$.tw. (2694)
3 salpingog$.tw. (227)
4 HSG.tw. (1452)
5 laparoscop$.tw. (117162)
6 exp LAPAROSCOPY/ (99372)
7 (tubal adj flush$).tw. (27)
8 (tub$ adj patency).tw. (994)
9 chromopertub$.tw. (130)
10 fertili$.tw. (119535)
11 or/1-10 (258375)
12 exp oil/ (14298)
13 oil$.tw. (124170)
14 exp ethiodized oil/ (577)
15 ethiodol.tw. (242)
16 iotrolan.tw. (222)
17 poppy.tw. (908)
18 exp ethiodized oil/ (577)
19 exp adipiodone/ (591)
20 exp WATER/ (277044)
21 IODIPAMIDE.tw. (134)
22 water.tw. (576375)
23 exp contrast medium/ (117267)
24 contrast medi$.tw. (22787)
25 (water adj soluble).tw. (35678)
26 (oil adj soluble).tw. (386)
27 aqueous.tw. (155448)
28 lipiodol.tw. (3652)
29 OSCM.tw. (16)
30 WSCM.tw. (16)
31 or/12-30 (987131)
32 11 and 31 (10395)
33 Clinical Trial/ (831601)
34 Randomized Controlled Trial/ (343448)
35 exp randomization/ (62313)
36 Single Blind Procedure/ (18367)
37 Double Blind Procedure/ (113645)
38 Crossover Procedure/ (39147)
39 Placebo/ (240637)
40 Randomi?ed controlled trial$.tw. (98971)
41 Rct.tw. (13930)
42 random allocation.tw. (1308)
43 randomly allocated.tw. (20183)
44 allocated randomly.tw. (1921)
45 (allocated adj2 random).tw. (712)

46 Single blind$.tw. (14252)
47 Double blind$.tw. (140404)
48 ((treble or triple) adj blind$).tw. (370)
49 placebo$.tw. (197255)
50 prospective study/ (252453)
51 or/33-50 (1358985)
52 case study/ (26347)
53 case report.tw. (258214)
54 abstract report/ or letter/ (891787)
55 or/52-54 (1170729)
56 51 not 55 (1321392)
57 32 and 56 (463)
58 (201308$ or 201309$ or 201310$ or 201311$ or 201312$).em. (109480)
59 2014$.em. (812650)
60 2014$.dp. (52878)
61 58 or 59 or 60 (924299)
62 57 and 61 (31)

Appendix 4. CENTRAL search strategy

1 HYSTEROSALPINGOGRAPHY/ or hysterosalpingog$.tw. (171)
2 salpingog$.tw. (7)
3 HSG.tw. (75)
4 laparoscop$.tw. (5936)
5 LAPAROSCOPY/ (2714)
6 Fallopian Tube Patency Tests/ (28)
7 (tubal adj flush$).tw. (4)
8 (tub$ adj patency).tw. (60)
9 chromopertub$.tw. (11)
10 fertili$.tw. (2691)
11 or/1-10 (8766)
12 OILS/ (107)
13 oil$.tw. (4703)
14 Ethiodized Oil/ (24)
15 ethiodol.tw. (2)
16 iotrolan.tw. (37)
17 poppy.tw. (18)
18 Iodized Oil/ (115)
19 IODIPAMIDE/ (18)
20 WATER/ (1487)
21 Contrast Media/ (2127)
22 contrast medi$.tw. (1449)
23 (water adj soluble).tw. (467)
24 (oil adj soluble).tw. (20)
25 aqueous.tw. (2238)
26 lipiodol.tw. (155)
27 OSCM.tw. (4)
28 WSCM.tw. (4)
29 or/12-28 (11564)
30 11 and 29 (106)
31 limit 30 to yr="2013 -Current" (5)

Appendix 5. PsycINFO search strategy

1 exp Fertility Enhancement/ or exp Infertility/ (1731)
2 hysterosalpingog$.tw. (3)
3 HSG.tw. (22)
4 laparoscop$.tw. (299)
5 (tubal adj flush$).tw. (0)
6 (tub$ adj patency).tw. (2)
7 chromopertub$.tw. (0)
8 fertili$.tw. (7390)
9 or/1-8 (8828)

10 oil$.tw. (3378)
11 Ethiodized Oil.tw. (0)
12 ethiodol.tw. (0)
13 iotrolan.tw. (0)
14 poppy.tw. (81)
15 Iodized Oil$.tw. (3)
16 IODIPAMIDE.tw. (0)
17 WATER.tw. (27085)
18 Contrast Medi$.tw. (95)
19 aqueous.tw. (503)
20 lipiodol.tw. (8)
21 OSCM.tw. (1)
22 WSCM.tw. (0)
23 or/10-22 (30736)
24 9 and 23 (90)
25 limit 24 to yr="2013 -Current" (10)

Appendix 6. Biological abstracts

1.HYSTEROSALPINGOGRAPHY/ or hysterosalpingography.mp. or hysterosalpingog$.tw.
2. salpingog$.tw.
3. HSG.tw.
4. laparoscopy adj3 dye).tw.
5. LAPAROSCOPY/
6. Fallopian Tube Patency Tests/
7. tubal adj flush$).mp. [mp=ti, kw, ab, bc, bt, bo, sh, hw, tn, ot, dm,mf, rw]
8. tub$ adj patency).tw.
9. or/1-8
10. OILS/
11. Ethiodized Oil/
12. Iodized Oil/
13. IODIPAMIDE/
14. WATER/
15. Contrast Media/
16. water adj soluble).tw.
17. oil adj soluble).tw.
18. lipiodol.tw.
19. OSCM.tw.
20. WSCM.tw.
21. Or/10-20
22. 9 and 21
23. exp clinical trials/
24. exp research design/
25. clinical trial.pt.
26. randomised controlled trial.pt.
27. (singl$ or doubl$ or trebl$ or tripl$).tw.
28. (mask$ or Blind$).tw.
29. 27 and 28
30. placebos/ or placebo.tw.
31. 23 or 24 or 25 or 26 or 29 or 30
32. 22 and 31

WHAT'S NEW

Date	Event	Description
16 April 2015	New citation required but conclusions have not changed	Our conclusions have not changed with the addition of one new study.
16 April 2015	New search has been performed	One study added (Lindborg 2009); contact details updated; one new comparison added (water-soluble contrast media versus

Date	Event	Description
		no treatment); risk of bias tables updated; tables of characteristics of included studies updated; review adapted to new format; summary of findings table added.

HISTORY

Protocol first published: Issue 2, 1996
Review first published: Issue 2, 1996

Date	Event	Description
13 June 2008	Amended	Converted to new review format.
16 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Lamiya Mohiyiddeen, Anne Hardiman, Cheryl Fitzgerald and Andrew Watson carried out this update in 2015. Andrew Watson was also an author of the original review, was involved in trial selection and data extraction of trials for the updated review and critically appraised previous updates. Neil Johnson conceptualised and carried out the updates of the former review: 'Oil-soluble versus water-soluble media for assessing tubal patency with hysterosalpingography or laparoscopy in subfertile women' (including trial selection and data extraction of trials for the updated reviews), and approved the 2015 update. Ed Hughes was author of the original review, commented on the updated review in 2007, and approved the 2015 update. Ben Mol joined the author group and commented on the 2007 update, and commented on and approved the 2015 update.

DECLARATIONS OF INTEREST

Neil Johnson and Andrew Watson were investigators in separate RCTs included in this review. Ben Mol is an investigator on ongoing trial Dreyer 2014 investigating oil-based versus water-based contrast media.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added one new comparison (water-soluble contrast media versus no treatment).

NOTES

This review was previously known as 'Oil-soluble versus water-soluble media for assessing tubal patency with hysterosalpingography or laparoscopy in subfertile women'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fallopian Tubes; Contrast Media [chemistry] [*therapeutic use]; Infertility, Female [*therapy]; Live Birth [epidemiology]; Oils; Pregnancy Rate; Randomized Controlled Trials as Topic; Solubility; Therapeutic Irrigation [*methods]; Water

MeSH check words

Female; Humans; Pregnancy